“Tear Film changes and Predictive factors of Symptomatic Dry Eyes and Visual Light Sensitivity after Laser Refractive Surgery”

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BY

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CERTIFICATE

This is to certify that the thesis entitled **Tear Film changes and Predictive factors of Symptomatic Dry Eyes and Visual Light Sensitivity after Laser Refractive Surgery** submitted by **Asra Fatima** bearing Registration Number **17MOPH01** in partial fulfilment of the requirements for the award of Doctor of Philosophy in the **School of Medical Science** is a bonafide work carried out by her under my supervision and guidance.

This thesis is free from Plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for the award of any degree or diploma.

Further, the student has the following publication(s) before submission of the thesis for adjudication and has produced evidence for the same in the form of an acceptance letter or a reprint in the relevant area of his research.

A) Journal Publications

1. Changes in the Tear Film and Meibomian Gland Morphology between Pre-clinical dry eye and Normal subjects represented by Ocular Surface Disease Index scores.

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B) Conference Presentations:

1. Indian Optometry Association 2020 – Virtual. *Presented a talk on "Post-Refractive Surgery Complications".*
2. ARVO India (Indian Eye Research Group) 2021- Virtual. *Presented a poster titled " Meta-analysis on Contact Lens Dropouts".*
3. American Academy of Optometry (AAO) 2022. San Diego, 28th Oct 2022. *Poster titled "Assessment of Visual Photosensitivity Thresholds after Laser Refractive Surgery using an Automated Photosensitivity Analyser". (Poster Board #181).*

Further, the student has passed the following courses towards the fulfilment of the coursework requirement for PhD.

S. No	Course No.	Name of the Course	Credits	Pass/Fail
1	OV801	Research Methods including Epidemiology	6	PASS
2	OV802	An Overview of Biostatistics	1	PASS
3	OV803	Health Communication an Introduction	1	PASS
4	OV804	Qualitative Research in Health Sciences	2	PASS
5	OV805	Bio and Research Ethics	1	PASS
6	OV806	Research in Special Circumstances	1	PASS

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DECLARATION

I, **Asra Fatima** hereby declare that this thesis entitled "**Tear Film changes and Predictive factors of Symptomatic Dry Eyes and Visual Light Sensitivity after Laser Refractive Surgery"** submitted by me under the guidance and supervision of Dr **Konda Venkata Nagaraju** is bonafide research work. I also declare that it has not been submitted previously in part or in full to this University or any other University or Institution for the award of any degree or diploma.

Date : 29/Aug/2022

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ABBREVIATIONS

TFOS – Tear Film and Ocular Surface Society

DEWS- Dry Eye Workshop

DED- Dry Eye Disease

OSD – Ocular Surface Disease

EDE- Evaporative Dry Eye

ADDE- Aqueous Deficient Dry Eye

MGD- Meibomian gland dysfunction

VDT- Visual Display Terminal

CL – Contact Lens

GHVD- Graft versus Host Disease

TNF - Tumour Necrosis Factor

MMP- Matrix MetalloProteinase

MUC5AC – Mucin 5 AC

OSDI- Ocular Surface Disease Index

DEQ- Dry Eye Questionnaire

DEQ-5- 5 item Dry Eye Questionnaire

MC- Mc Monnie's Questionnaire

OCI- Ocular Comfort Index

SANDE- Symptom Assessment in Dry Eye

SPEED- Standard Patient Evaluation of Eye Dryness

DEQS- Dry Eye-Related Quality of Life Score

IDEEL- Impact of Dry Eye in Everyday Life

OST- Ocular Surface Temperature

TMH- Tear meniscus height

TMA- Tear meniscus area

OCT- Optical Coherence Tomography

CLSM- In-vivo confocal laser scanning microscopy

HLA- DR- Human leucocyte Antigen -DR

AK- Astigmatic keratotomy

LASEK- Laser-Assisted Sub-Epithelial Keratectomy

PRK- Photorefractive Keratectomy

LASIK- Laser Insitu Keratomileusis

SMILE- Small Incision Lenticule Extraction

OPA- Ocular Photosensitivity Analyser

NIBUT- Non-Invasive Break-up time

CVS-Q – Computer Vision Syndrome Questionnaire

MG- Meibomian Gland

ICC- Intraclass Correlation Coefficient

UL- Upper Lid

LL- Lower lid

IR- Infrared

UCVA – Uncorrected Visual Acuity

CDVA- Corrected Distance Visual Acuity

OPA- Ocular Photosensitivity Analyser

VPT- Visual Photosensitivity Threshold

HIT-6 - Headache Impact Test-6

VLSQ-8- Visual Light Sensitivity Questionnaire 8

VLS- Visual Light Sensitivity

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ABSTRACT

This thesis aimed to evaluate the changes in the tear film and MG morphology among subjects with pre-clinical dry eye and compare them with normals defined by their OSDI scores. Furthermore, the tear film changes after laser refractive surgery among symptomatic dry eyes were evaluated along with the predictive factors for the occurrence of transient and persistent symptomatic dry eyes. Also, changes in the visual light sensitivity after laser refractive surgery were assessed using an automated Ocular Photosensitivity Analyser (OPA).

In this thesis, a prospective study was conducted at the University of Hyderabad on normal subjects presenting for a regular eye examination. Tear film such as non-invasive break-up time (NIBUT), tear meniscus height (TMH), Schirmer's test and corneal staining and MG morphology (MG length, MG width, MG loss and tortuosity) were assessed and the subjects were categorised into two groups based on an OSDI threshold score of ≥13. Among subjects presenting for laser refractive surgery, OSDI scores and other tear film tests such as NIBUT, TMH and Schirmer's test were performed preoperatively on the day of surgery and postoperatively at 1 week. Subjects were categorised into three dry eye groups based on the OSDI threshold score of ≥13 at the pre and postoperative visit as, no dry eye, transient symptomatic dry eye and persistent symptomatic dry eye. For assessing visual light sensitivity, visual photosensitivity thresholds (VPT) were assessed preoperatively on the day of surgery and postoperatively at 1 week and 1 month.

It was found that NIBUT was lower and the MG length of the lower lid was lesser among subjects with pre-clinical dry eye when compared to normals. Other tear film tests and MG morphology did not vary significantly between the groups. Among laser refractive

surgery subjects, it was found that 24% of them had symptomatic dry eyes before laser refractive surgery based on the OSDI threshold score. OSDI scores and tear film tests such as NIBUT and Schirmer's test were significantly reduced among the persistent symptomatic dry eye when compared to no dry eye. Predictive factors for the occurrence of persistent symptomatic dry eye were the preoperative OSDI scores and the NIBUT. It was found that the visual photosensitivity thresholds were reduced after laser refractive surgery at postoperative 1 week and then returned to near normal values by 1-month postoperative visit. At the postoperative 1-week visit, the binocular VPT was significantly reduced than the monocular VPT.

The studies from this thesis conclude that the subjects with pre-clinical dry eyes defined by the OSDI score of ≥13 have early signs of dry eyes such as lower NIBUT and lesser MG length of the lower lid. Hence, evaluating OSDI scores along with NIBUT and MG imaging might be helpful. Similarly, subjects presenting with dry eye symptoms have significantly reduced tear stability and tear secretions after laser refractive surgery. Hence, it is necessary to ascertain that the subjects do not have any dry eye symptoms preoperatively by assessing the symptoms, tear stability and secretions. It was also observed that the visual light sensitivity was increased (measured as a decrease in the VPT) after laser refractive surgery at the early postoperative visit. However, this becomes near normal (seen as an increase in VPT) by a postoperative 1-month visit.

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Chapter-1: Introduction

1.1 Dry Eye

A dry eye is an ocular condition where the tear film is disturbed due to alteration either in the tear volume or thickness; or due to an imbalance between the layers of the tear film. It is a significant health concern even today, which leads to poor quality of life. [1] Thirty years ago, it was formally defined as a disease, after which the field had rapidly developed.[2]

1.1.1 Definition of Dry Eye

Various definitions were published and modified based on the understanding of the disease. The first definition was published in 1995,[3] where the dry eye was defined as *''Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort."*

The definition was later modified in 2007 by TFOS DEWS I[4] as *''Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased tear film osmolarity and inflammation of the ocular surface.''*

Recently, this definition was revised in 2017,[2] where TFOS DEWS II defined dry eye as "*a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."*

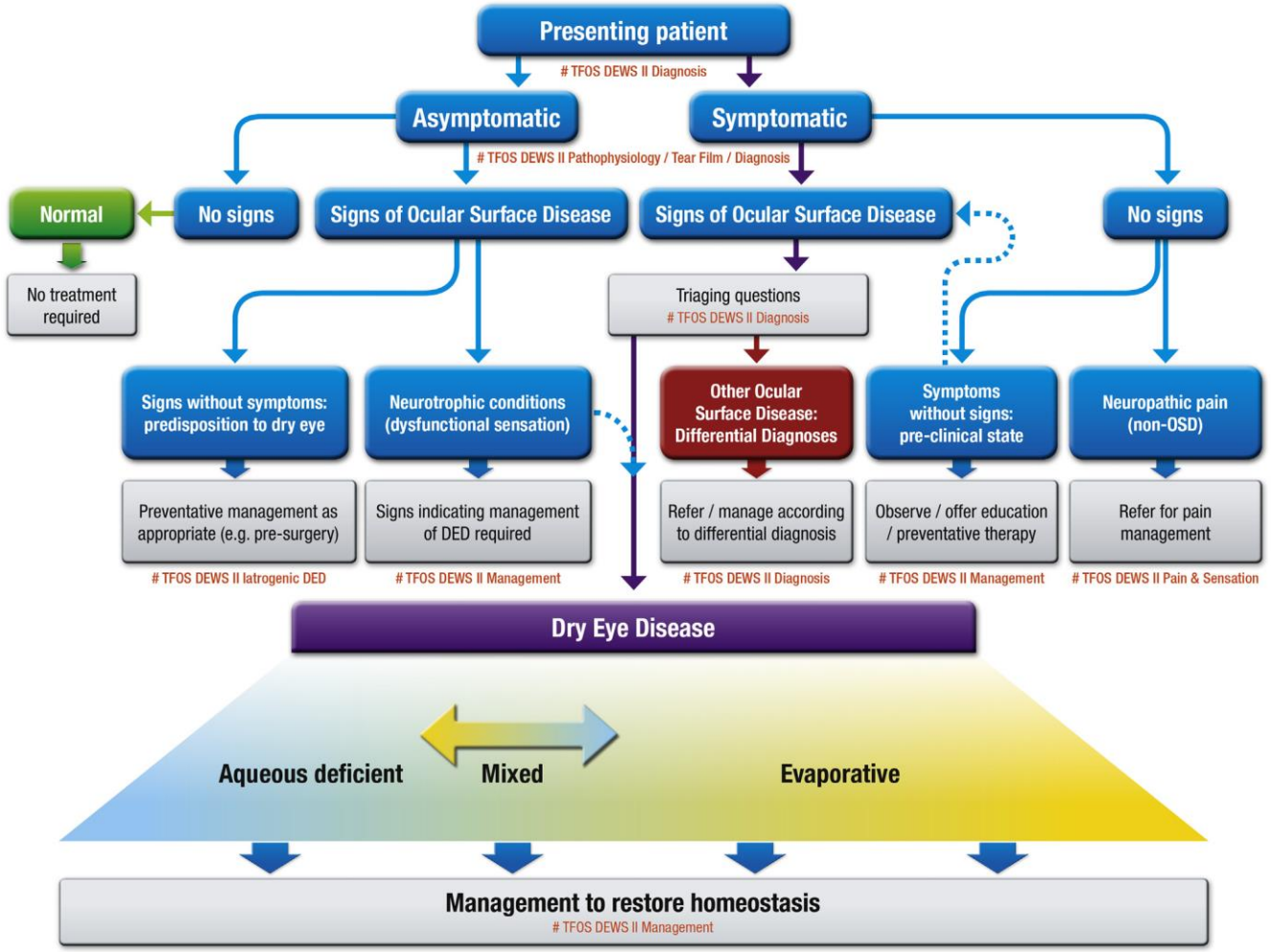
1.1.2 Classification of Dry Eye

Various classifications were specified for the dry eye based on insight into the disease. As the definition of dry eye has been updated, the classification was also updated. **Figure 1** shows the recent classification of dry eye as per the 2017 TFOS DEWS II report.[2] This classification has two components: 1) Classification based on the clinical decision made by a clinician and 2) Classification based on the aetiology of the disease.

In the upper component, the classification is based on symptoms, grouped as symptomatic and asymptomatic. Then, based on clinical tests, it is further classified as no signs or the presence of signs of ocular surface disease. When there are no signs or symptoms, then it is normal. Among those with signs and without symptoms could be those with lesser corneal sensitivity or prodromal signs.[5] Therefore, they are at risk of developing manifest DED with time. Symptomatic patients without clinical signs indicate a pre-clinical dry eye state or the presence of neuropathic pain. On the other hand, symptomatic patients who demonstrate clinical signs are discriminated from the other ocular surface diseases by asking triaging questions[6] and are then managed or treated according to differential diagnosis.

Based on aetiology, the lower part of the classification is predominantly classified as Evaporative dry eye (EDE) and Aqueous dry eye (ADE).[7] EDE is caused by lid-related factors, such as the meibomian gland and blink rate and ocular surface-related factors, such as mucin and contact lens. Whereas changes in the lacrimal gland cause ADE. Among all, the most prevalent and commonly seen is Evaporative Dry Eye.

Figure 1: Classification of dry eye disease as per DEWS-II report. [2] It shows a two-way classification with decisions made by a clinician (from the top) and based on aetiology (from the bottom)



1.1.3 Prevalence and Risk Factors:

DEWS II report has conducted a literature review to report the prevalence estimates for dry eye disease in the population.[8] They have reported that the prevalence of the disease range between 5% to 50% with symptoms, with or without signs. They have also reported a prevalence of up to 75% in specific populations, where the diagnosis was primarily based on signs. This prevalence of dryness increase with increase in age. Females showed a higher prevalence of dryness than males. The prevalence of DED is more elevated in Asians than in Caucasian populations.

There are various risk factors for developing DED given in **Table *1***, among which few are modifiable, and few are non-modifiable. An increase in age is a non-modifiable and most common risk factor for DED.[9–11] Similarly, the female gender is more at risk for DED than males.[12–14] Meibomian gland dysfunction (MGD) is at risk of developing DED, as studies have found associations between MGD and EDE.[4,15,16] Asian race was found to have a higher risk of DED when compared to other races.[17,18] Contact lens (CL) wearers are at the risk of developing DED, as they report increased symptoms of dryness compared to non-contact lens wearers.[19,20]

The use of a visual display terminal (VDT) is one of the significant risk factors for DED.[21] With VDT use, there is a decreased blink rate, thereby leading to evaporation of the tear film, instability and dry eye symptoms.[22–24] In environments such as low humidity[25] and highly polluted areas,[26] the risk of developing DED is higher. Among nutritional intake, deficiency of Vitamin A is associated with DED,[27] and this deficiency of Vitamin A is most commonly seen in African countries. Diabetes is found to be associated with dry eye in most of the studies.

Sjogren's syndrome, a chronic autoimmune disorder, is predominantly associated with a dry eye, particularly the aqueous deficient dry eye, as the lacrimal glands are affected. [28,29] Prevalence of DED is higher in ocular Graft versus Host Disease (GVHD), where the ocular surface is affected.[30,31] Post- Refractive surgery, dry eye is one of the most common complications seen. Among all refractive surgery procedures, Laser In situ Keratomileusis is most associated with dry eye as the corneal nerves are damaged, leading to neuropathic dry eye.[32] Several psychological disorders such as anxiety and depression, are most commonly associated with DED.[33,34] Apart from all these factors, heredity and genetics is also found to be risk factor for dry eye[35,36], however, very little is known.

Table 1: Risks factors for dry eye

Age	Refractive surgery
Sex	Diabetes
Meibomian gland dysfunction	Hematopoietic stem cell transplantation
Asian Race	Vitamin A deficiency
Contact Lens wear	Environmental exposures
Visual display / Computer use	Affective and somatoform disorders
Sjogren's syndrome	Heritability and genetic risk factors

1.1.4 Pathophysiology

The TFOS DEWS-II reported that the hyperosmolarity of the tear film hyperosmolarity, together with the tear film instability are the key drivers of DED.[37] In EDE, tear hyperosmolarity occurs because of the tear film evaporation with the presence of normal lacrimal function. Whereas in ADDE, tear film hyperosmolarity occurs because of decreased lacrimal secretion with the presence of an average rate of tear evaporation.[38] Lipid layer deficiency of tear film coexisting with MGD is a typical cause of EDE and decreased tear secretion because of damage to the lacrimal gland is a typical example of ADDE. However, most forms of DED are evaporative in nature, as without tear film evaporation, hyperosmolarity cannot occur. In cases where tear film evaporation is increased by external factors such as temperature and humidity or personal factors such as blink rate, blink pattern, and effects of systemic medications on the tear film, it is termed "hyper-evaporative dry eye".[38]

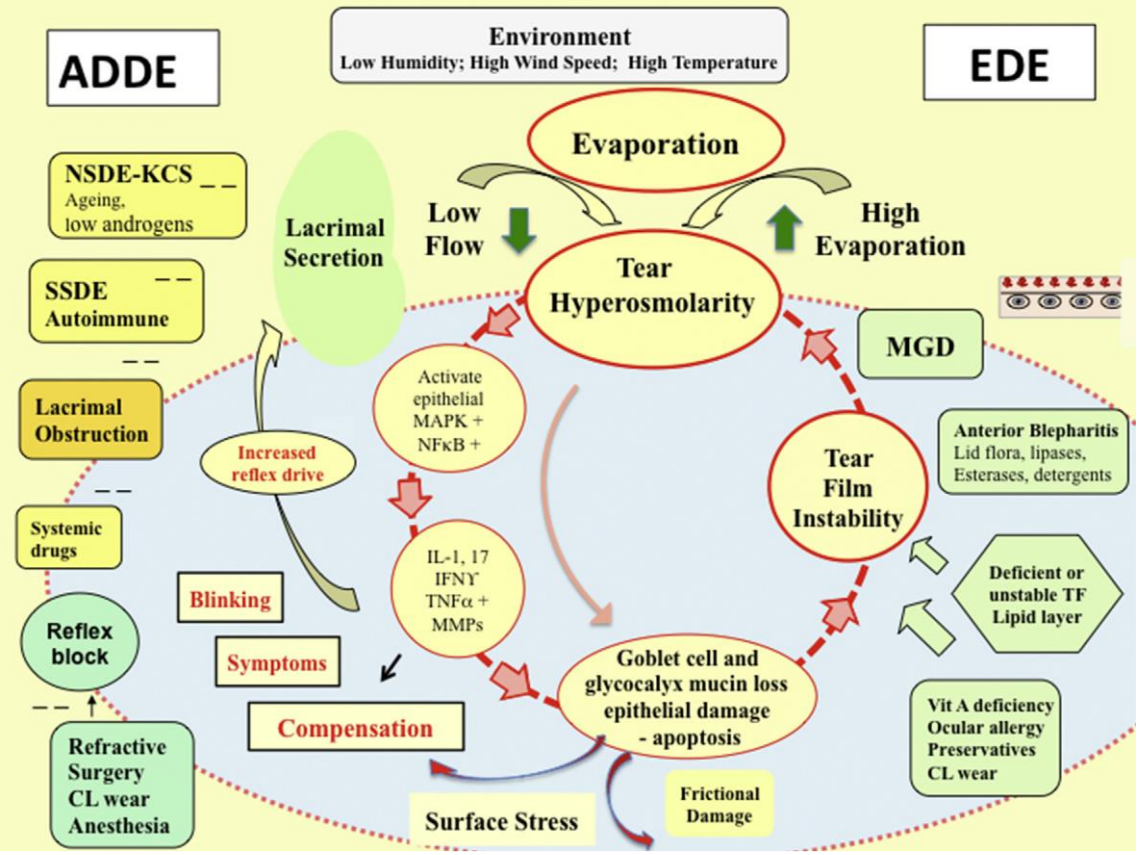
1.1.4.1 The Vicious Circle of dry eye:

This is the basic and simple model of DED[39] **(*Figure 2*),** where hyperosmolarity of tear film is the starting point, which transmits a series of events leading to the ocular surface damage. At first, a cascade of events occurs in epithelial cells of the ocular surface, leading to the production of inflammatory cytokines (IL-1, IL-1a IL-1b, tumour necrosis factor- a TNF-a) and proteases (matrix metalloproteinase 9 (MMP9)).[40] These mediators, along with hyperosmolarity of tear film, lead to decreased mucin expression from glycocalyx, leading to a loss of goblet cells. This goblet cell loss is a usual feature seen in every form of DED,[41,42] which is reflected by the reduction of MUC5AC in tears.[43,44] Decreased mucin expression is

evidence for the occurrence of ocular surface staining and altered surface wetting, thereby leading to early tear film breakup.

In MGD-related dry eye, tear hyperosmolarity occurs due to the deficiency of the lipid layer of the tear film. In ADDE, tear hyperosmolarity occurs due to a blocked sensory drive to the lacrimal gland, which is necessary for maintaining ocular homeostasis. Due to such a reflex block, dry eye can be caused by chronic abuse of topical anaesthetics, trigeminal nerve damage and refractive surgery.[38] Various systemic medications, such as antihistamines, beta-blockers, antispasmodics, diuretics and a few other psychotropic drugs, cause a reduction in lacrimal gland secretion, which are also the risk factors for DED.

Figure 2: Vicious circle of dry eye[38], showing the pathophysiology of dry eye disease as a series of events happening in Evaporative Dry Eye (EDE) and Aqueous Deficiency Dry Eye (ADDE)



1.1.5 Symptoms and signs of dry eyes:

Symptoms of dry eyes can range from mild, episodic, severe and chronic. The primary and most common symptom is ocular discomfort,[3] which has also been included in the recent definition of dry eye.[2] In ocular discomfort patient experiences ocular pain, foreign body sensation, redness, burning or stinging sensation and in severe cases leads to light sensitivity or photophobia. Besides ocular discomfort, visual disturbance such as transient blurring of vision caused by tear film disruption is also reported.

Signs of dry eyes include the presence of a partial blink or a low blink rate. Slit lamp examination shows the presence of blepharitis, meibomitis, conjunctival hyperaemia, thinner tear film, and the presence of mucus strands on the cornea. Other signs seen in assessing the tear film include poor tear film stability with a tear film break-up time of <10 seconds, shorter tear meniscus height of <0.2 mm, presence of corneal and conjunctival staining, thinner oily layer indicated by closed or open meshwork pattern on interferometry, wetting on Schirmer's strip less than 10mm in 5 minutes and increased tear osmolarity.

1.1.6 Diagnostic methods:

Although various tests and questionnaires are available to detect dry eyes based on signs and symptoms. Among all the diagnostic tests available[6] **(*Table 2*),** few are invasive, which come in contact with the eye, and few are non-invasive. Invasive tests have their disadvantages of having low reproducibility and inter-observer repeatability[45] and cause ocular surface changes while performing the procedure.[46] Hence, it is suggested to perform the tests from the least invasive to the most invasive ones.[47] For an accurate diagnosis, there is no gold standard procedure or test available to detect or diagnose dry eye until recent.

Table 2: Tear film tests for diagnosing dry eye disease

Tear film assessment	**Diagnostic tests**
Symptoms	Questionnaire
Tear film stability	Fluorescein tear breakup time Non-invasive tear breakup time Thermography
Tear volume	Tear meniscus assessment Phenol red thread test Schirmer's test
Tear film composition	Tear film osmolarity Tear film ferning
Damage to ocular surface	Impression cytology In vivo confocal microscopy Ocular surface sensitivity
Inflammation of ocular surface	Matrix metalloproteinases Cytokines and chemokines. Ocular surface immune markers.
Eye lid aspects	Interferometry Meibography Blink analysis

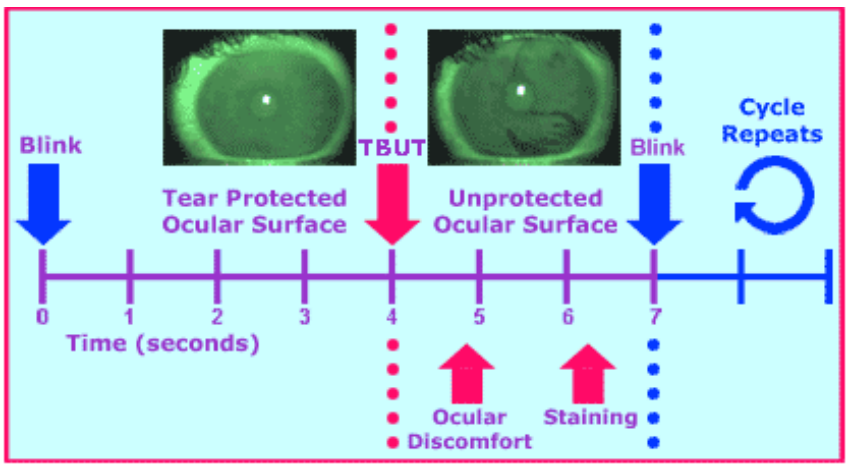
1.1.6.1 Questionnaires for dry eye assessment:

Many questionnaires have been developed to assess the patient related dry eye symptoms. Most frequently used dry eye questionnaires include: Ocular Surface Disease Index (OSDI)[48], Dry Eye Questionnaire (DEQ),[49] 5 item Dry Eye Questionnaire (DEQ-5),[50] Mc Monnie's Questionnaire (MC),[51] Ocular Comfort Index (OCI),[52] Symptom Assessment in Dry Eye (SANDE),[53] Standard Patient Evaluation of Eye Dryness (SPEED),[54] Dry Eye-Related Quality of Life Score (DEQS),[55] Impact of Dry Eye in Everyday Life (IDEEL).[56] Among all these questionnaires the most commonly used questionnaire is OSDI.

1.1.6.2 Tear breakup time:

This is the most frequently performed dry eye test for assessing the tear film stability. It is calculated as the time between the first blink and the appearance of the first break-up in the tear film. It can be performed invasively by instilling fluorescein in the eye where the break up in tear film is seen as a black dry spot (***Figure 3***), or by non-invasive technique by imaging the tear film, where the tear break up is seen as an irregularity in the illuminated grid pattern. Usually, a cut-off value of fewer than ten seconds is indicated for the diagnosis of DED.[57]

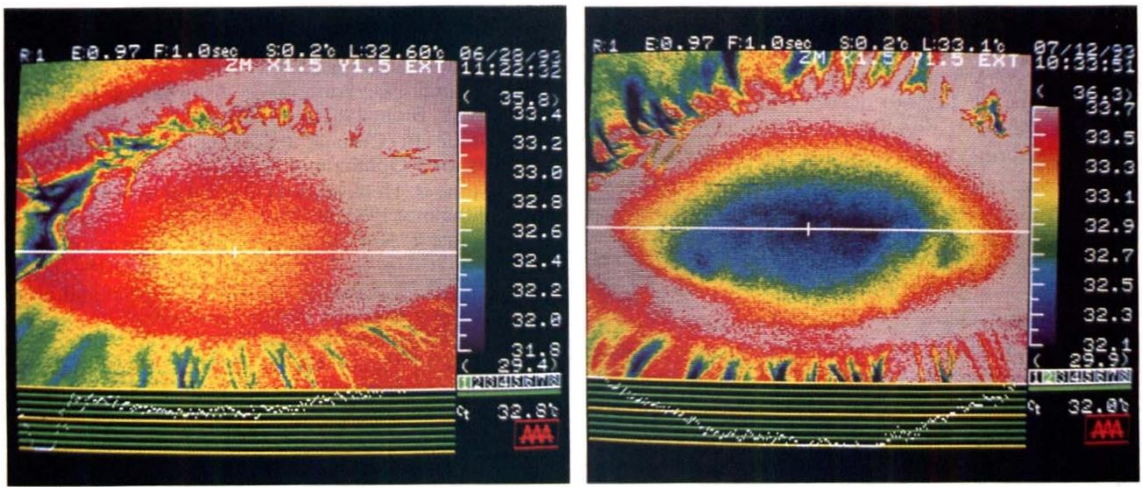
Figure 3: Tear film break up time[58] is measured as the time gap between the first blink and the appearance of the dark spots in the tear film.



1.1.6.3 Ocular thermography:

Infrared thermography is a novel method to evaluate the tear film stability and tear evaporation by measuring the Ocular Surface Temperature (OST). [192], Where evaporation of tear film leads to the cooling of ocular surface temperature.[59] This ocular surface cooling was found to be faster in DED patients, where the OST shows a larger decrease at 10 seconds after eye-opening, which is because of a greater rate of evaporation (***Figure 4***).[59–61] Sensitivity and specificity values for ocular thermography were reported to be around 80%.[60,61]

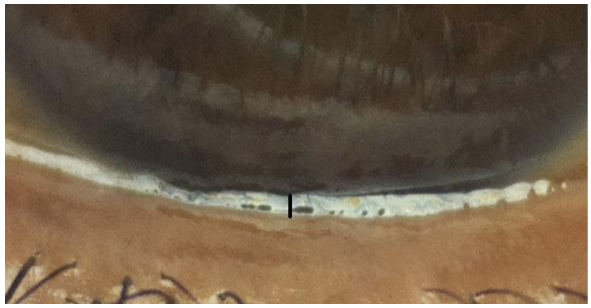
Figure 4: Ocular surface thermography of normal eye (left) and dry eye (right)[62], where ocular surface temperature appears cooler (cooler colours) than normal eyes due to faster evaporation.



1.1.6.4 Tear meniscus assessment:

The tear meniscus is the reservoir of tears located at the upper and lower lid margins, contributing to the volume of the tear film (***Figure 5***). Meniscometry is the assessment of tear meniscus. It can be either assessment of tear meniscus height (TMH) or tear meniscus cross-sectional area (TMA). Various techniques are available to measure TMH or TMA. The simplest of them is slit-lamp meniscometry, where TMH is judged on a slit lamp by comparing it to the adjusting slit-lamp beam height, however, this technique had poor inter-visit repeatability.[63] Current imaging techniques include Anterior segment Optical Coherence Tomography (OCT), Keratograph 5M, Tearscope and EASYTEAR view+.[64,65] Mean values for inferior TMH range between 256 ± 57 μm to 400 ± 170 μm, whereas it is lesser in dry eye patients.[64,66,67]

Figure 5: Normal tear meniscus height, measured using EASYTEARview+ at the lower lid near the central cornea.



1.1.6.5 Phenol red thread test:

This test measures the tear volume, where a yellow thread is placed in the lower lid for 15 seconds and the length of wetting of the thread is recorded in mm. A cut-off value of

20 mm was reported to discriminate normals from DED subjects.[68] This test is not commonly used as a diagnostic test for dry eye.

1.1.6.6 Schirmer's test:

It measures the reflex tears, whereas the tear meniscus represents the basal tear volume.[69] The Schirmer's strip is placed in the lower conjunctival fornix at the temporal one-third. The wetting of this strip is measured for 5 minutes and is recorded in mm. It is most commonly performed without instilling anaesthetic drops, however, few articles have reported using anaesthetic drops and by nasal stimulation.[70,71] Various diagnostic cut-off values were reported from 5 mm in 5 minutes,[38] to 10 mm in 5 minutes,[72] however most commonly used cut-off value for dry eye diagnosis is the wettability of strip less than 10mm in 5 mins.

1.1.6.7 Tear film osmolarity:

Tear osmolarity has been reported as the single best measurement for detecting, diagnosing and classifying DED [12,13,246]. It was found to be highly correlated with the severity of DED.[11] Tear osmolarity is the most commonly measured used TearLab osmolarity (Tearlab Inc., San Diego, USA) (***Figure 6***). TearLab osmometer uses a "lab on a chip" at the tip of a handheld sampler, which measures the electrical impedance of the tear fluid sample in a tiny channel in the chip, which then calculates and displays the osmolarity measurements.[73]

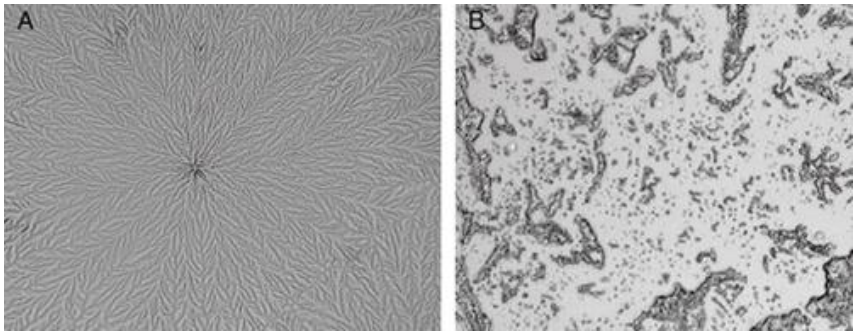
Figure 6: Tear osmolarity measured using Tear lab osmolarity test[73]

Normal tear film osmolarity values ranges from 270 to 315 m Osm/L.[74] Tear osmolarity values are higher in dry eye patients than normals.[74]

1.1.6.8 Tear film ferning:

Tear ferning tests provides a gross estimation of tear composition at biochemical level. The tear film is allowed to dry on a glass plate under room temperature and humidity, where ferning occurs (***Figure 7***).[75] This pattern of ferning is dense among healthy individuals, whereas in dry eyes this pattern is either fragmented or absent.[76] Sensitivity and specificity of tear ferning test was greater than 80% in both Sjogren's syndrome,[77,78] and rheumatoid-induced keratoconjunctivitis sicca.[79]

Figure 7: Tear ferning pattern seen under high magnification microscope.[75] Left image shows the dense pattern from a normal eye and the right image shows the broken pattern from dry eyes



1.1.6.9 Impression Cytology:

Impression cytology is most commonly performed for ocular surface disorders[80] as goblet cell changes are observed in DED and various other related conditions. Epithelial cells from the superficial layers are removed by using cellulose acetate filters or biopore membranes, which are later analysed using various laboratory methods.[81]

1.1.6.10 In-vivo confocal microscopy:

In-vivo confocal microscopy is a newer method to measure the ocular surface damage occurred at the cellular level.[82,83] It also helps in imaging the corneal nerve damage that occurs in dry eye disease.[84,85]

Currently available techniques for imaging corneal nerves and tissues include in-vivo confocal laser scanning microscopy (CLSM), using the Heidelberg Retinal Tomograph and the Confoscan.[86,87] Although, invasive in nature, they provide good quality images to study morphological changes in cells and nerves among various ocular conditions.

1.1.6.11 Corneal sensitivity:

Corneal sensitivity is an objective measurement of corneal sensation. Loss of corneal sensation is also one of the risk factors for DED. Most commonly corneal sensitivity is measured using a Cochet-Bonnet esthesiometer.[88] Few non-contact air jet esthesiometers are also available for measuring corneal sensitivity, however, they are not much used.[89,90]

1.1.6.12 Tear film biomarkers:

Tear film proteins present in the tears also help in the diagnosis of dry eye. These proteins are lesser in dry eyes when compared to normals.[91] Whereas, proinflammatory and inflammatory markers such as matrix metalloproteinase 9 (MMP-9) were higher in dry eyes.[92] To detect this, laboratory tests are needed for tear collected. However, a diagnostic device was developed named Inflamma Dry Detector (InflammaDry, Rapid Pathogen Screening, Inc, Sarasota, FL, USA) which could detect the level of MMP-9 in 10 min.[93]

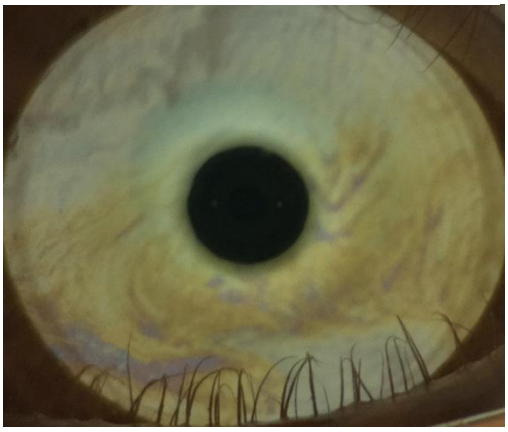
As cytokines and chemokines also take part in the inflammation process, these levels are reported to be varied among dry eyes. Biomarkers such as interleukin-1Ra and interleukin-8

were found in the tears of patients with dry eye.[94] Similarly, cytokines such as interleukin-17, interleukin-6 and tumour necrosis factor-alpha were found to be elevated in Sjogren syndrome patients with dry eye.[95] Immune markers such as HLA-DR expression have been studied and found to be correlated with increased severity of the dry eye.[96]

1.1.6.13 Interferometry:

The superficial lipid layer of tear film produces a fringe pattern which can be viewed using interferometry (***Figure 8***). There are various lipid layer patterns generated based on the thickness,[97] which includes open meshwork, closed meshwork, wave pattern, amorphous pattern and colour fringe pattern.[98] Thinner lipid layer thickness indicates the presence of MGD, thereby leading to dry eyes.[99] Currently available devices to measure lipid layer thickness include LipiView (TearScience Inc., Morrisville, NC, USA), which measures the lipid layer thickness in the inferior cornea.

Figure 8: Colour fringe pattern of lipid layer viewed using interferometry.

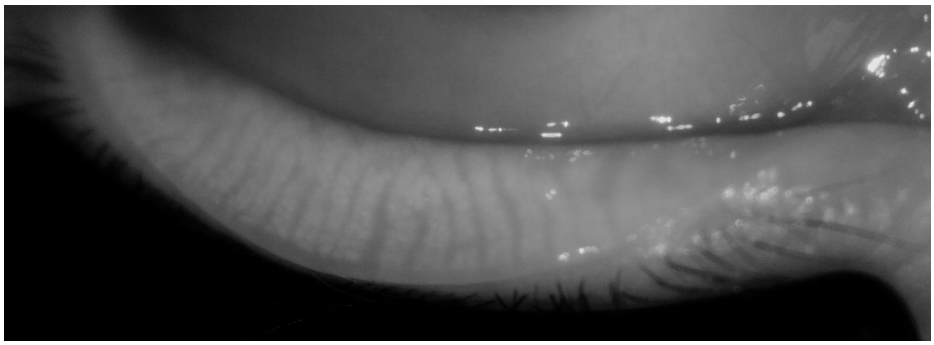


1.1.6.14 Meibography:

Meibography is the imaging of meibomian gland structure and morphology. Infra-red imaging systems help in the visualisation of meibomian glands (**Figure *9***). Various non-invasive infra-red imaging devices have been developed recently to study the meibomian gland morphology.[100,101] Meibomian gland loss is usually expressed in percentage as the ratio of loss area and the total tarsal area.[102] Various grading scales have been proposed,[103] however the most commonly used one is the meiboscale,[104] where: grade-0 indicates no loss

of MGs, grade-1 indicating loss ≤ 25%, grade-2 indicating MG loss≤50%, grade-3 indicating MG loss≤75%; and grade-4 indicating MG loss ≤ 100%. This scoring system can be used to document the presence of MGD and its progression.[105]

Figure 9: Meibography of lower lid imaged using EASYTEAR view+



1.1.6.15 Blink analysis:

Blinking plays an important role to maintain ocular surface health by removing debris and protecting against trauma. A blink pattern can be a complete or partial blink, which is seen among most of the healthy population.[106,107] The normal blink rate is reported to be around 10 to 15 blinks per minute.[108] Blink rate and the pattern are found to be associated with dry eyes.[108,109]

1.2 Laser Refractive Surgery:

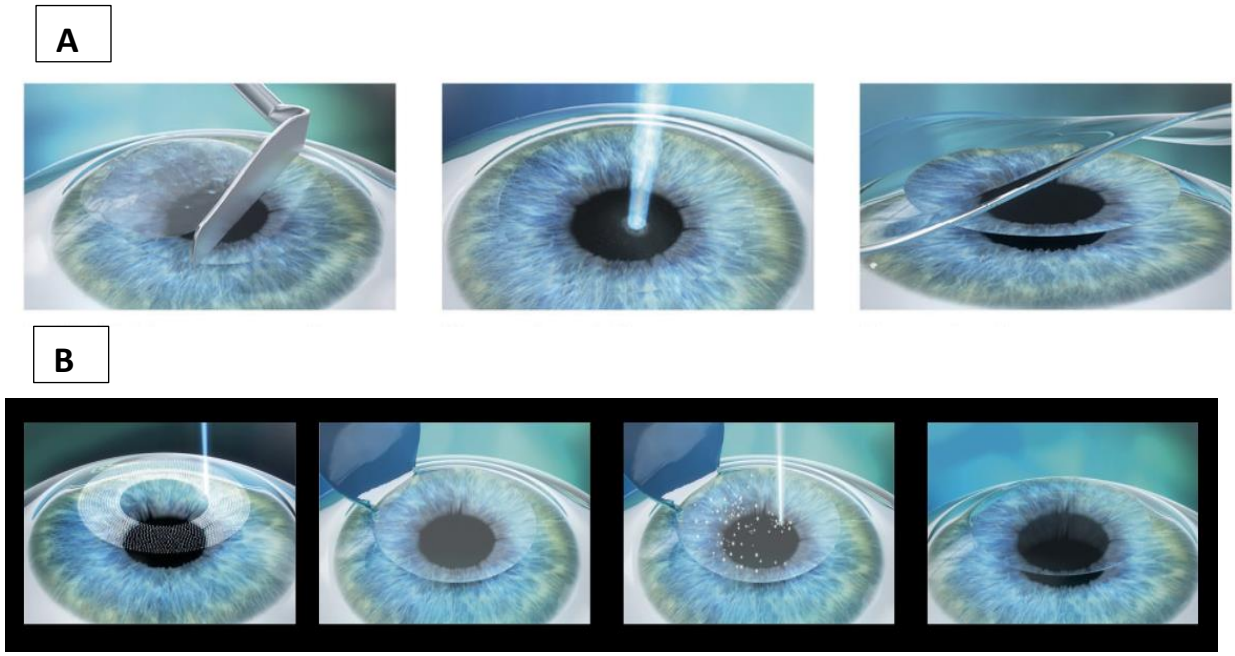
It is a surgical procedure to correct the eye's refractive error. It is an alternative to glasses or contact lenses but corrects the refractive error permanently by reshaping the corneal curvature. It was reported that 20-25 million eyes are treated with laser vision correction by 2021.[110]

1.2.1 Types of laser refractive surgery:

There are various refractive surgery procedures which include Radial Keratectomy, Astigmatic keratotomy (AK), Laser Assisted Sub-Epithelial Keratectomy (LASEK), Photo Refractive Keratectomy (PRK), Laser Insitu Keratomileusis (LASIK) and Small Incision Lenticule Extraction (SMILE).[111,112] Among these, the most commonly performed procedures include PRK and LASIK.

In PRK, the superficial layer of the cornea is removed either by scrapping or alcohol, then the laser is applied to correct the refractive surgery. Finally, a bandage contact lens (BCL) is placed on the eye to promote the healing of the epithelial layer (***Figure 10***). For the LASIK procedure, a flap is created either manually using a microkeratome or using Femto Laser, which is lifted up, then the laser is allowed to correct the refractive error of the eye, and finally, the flap is replaced back in its place (***Figure 10*****)**

Figure 10: Laser refractive surgery procedures: A) Photorefractive keratectomy, showing the scrapping of the epithelium (left), followed by applying excimer laser (middle), then bandage contact lens is placed to promote epithelial healing. B) Femtosecond LASIK, where the flap is created using Femtosecond laser (left), then the flap is lifted and the laser is applied (middle) and the flap is then placed back. [Image source: www.zeiss.com]



1.2.2 Indications and Contraindications of laser refractive surgery

Indications for laser refractive surgery, in general, include age greater than 18 years of age with stable refractive error for at least one year, corneal thickness more than 480 microns, mesopic pupil size of greater than 7mm, steep keratometry less than 48D and corneal irregularity is seen on ocular topography.

Contraindications of laser refractive surgery can be absolute or relative.[111,113,114] Absolute contraindications for laser refractive surgery include ocular conditions such as corneal ectasia, symptomatic cataract, uncontrolled glaucoma, exudative macular degeneration, abnormal corneal wound healing, corneal ulceration, recurrent corneal

erosions, and thinner corneas and systemic conditions such as autoimmune diseases, diabetes mellitus with reduced corneal sensation, pregnancy and thyroid orbitopathy. Relative contraindications include irregular corneal astigmatism, family history of glaucoma, use of any medication that causes dryness (those with anticholinergic effects, sympathomimetics, clonidine), lid conditions such as blepharitis and meibomitis, corneal pathologies such as epithelial basement membrane dystrophy or history of herpes simplex keratitis and systemic conditions such as early diabetes.

1.2.1 Side-effects of laser refractive surgery:

Side effects after laser refractive surgery occur for a period of time, which then resolves during the healing process. The most common side effects seen after laser refractive surgery include in the early postoperatively include ocular pain, discomfort, light sensitivity and vision fluctuations, whereas dry eyes, haloes, and night vision disturbances occur during the late postoperative period.[115] The incidence of night vision disturbance is reported as 25.6% 1 month and 4.7% at 12 months after laser refractive surgery.[116]

1.3 Review of Literature:

1.3.1 Literature on the tear film and MG morphology changes among dry eyes:

Differences in the tear film among subjects diagnosed with dry eyes (based on symptoms and signs) are well known as per the DEWS-II report.[2,6] These changes include poor tear film stability with a tear break-up time of <10 sec, wetting of Schirmer's strips less than 10 mm in 5 minutes, lower tear meniscus height of < 0.2 mm, presence of corneal and conjunctival staining, increased tear film osmolarity, less tear proteins, increase in proinflammatory and inflammatory biomarkers such as interleukin-1, interleukin-6,

interleukin-8, MMP-9, as well as an increase in cytokines and chemokines such as tumour necrosis factor (TNF) alpha and neuropeptide Y.[6,91,93,94,116–120]

Meibomian gland dysfunction (MGD) is one of the common reasons for the unstable tear film.[15] Vital signs for MGD are morphological changes,[101] which occur before the onset of symptoms.[121] These meibomian gland changes increase with an increase in age.[101] It was also reported that the dry eye subjects showed a significant increase in MG loss, especially in the lower lid[122] and this loss significantly correlated with tear film and dry eye symptoms.[123] Also, MG morphology was reported to be altered among evaporative dry eye patients compared to normals without dry eyes.[124] MG irregularity might predict the presence of MG dysfunction, and its effect on tear film.[125] MG morphological changes are also seen in patients presenting from refractive surgery[126] and there exists a difference in meiboscale between younger and older adults.[126,127]

1.3.1.1 Studies on symptomatic or pre-clinical dry eyes:

The tear turnover rate among symptomatic dry eyes was found to be lesser compared to asymptomatic controls.[128] This study has defined symptomatic dry eyes based on the positive Mc Monnie's dry eye questionnaire and the use of lubricating eye drops. Kobia-Acquah E et al[129] estimated the prevalence of pre-clinical dry eyes based on the OSDI threshold score and found it to be around 63% in the Ghanaian population. Ystenæs AM et al.[130] categorised the subjects based on OSDI threshold scores and found that the tear breakup time was different between these subjects and normals. They have also reported that OSDI ≥ 13 showed a diagnostic ability to discriminate between patients with fluorescein breakup time < 10 seconds.

1.3.2 Literature on Incidence, Prevalence, Predictive factors and tear film changes after laser refractive surgery

As discussed earlier, that dry eye is one of the most common side effects following laser refractive surgery. It was found that approximately 30% of patients referred to tertiary eye care following LASIK had dry eyes.[131,132] Edward YW et al.[133] reported that up to 95% of patients report at least one dry-eye-related symptom immediately following LASIK surgery, which recovers 3-6 months after surgery. Prevalence of dry eye varies between 40 and 59% 1 month, 10-40% at 6 months after refractive surgery.[134,135] Studies have also reported the incidence rates of dry eyes after laser refractive surgery. Where Shoja MR et al.[136] reported that 20% of the sample had chronic dry eye persisting after LASIK. Similarly, Hovanesian JA et al.[137] reported an incidence of dryness symptoms of 43% and 48% at 6 months post-PRK and LASIK respectively. However, Bower KS et al.[138] reported a lesser incidence of chronic dry eye 12 months post LASIK and PRK, which was around 5%. It was also found that Asian eyes have more prevalence of ocular dryness before and after refractive surgery than Caucasian eyes.[139]

Studies have also reported predictive factors for the occurrence of chronic dry eye, where preoperative Schirmer's test can predict its occurrence after PRK and preoperative Schirmer's test along with ocular surface staining can predict the occurrence of chronic dry eye after LASIK.[138,140] Doodley I et al.[141] found that tear osmolarity was one of the significant predictors of dry eye after LASEK and LASIK. It is also important to treat lid conditions such as blepharitis and meibomitis to prevent evaporative dry eye.

Various studies have reported the changes in the tear film after laser refractive surgery which are similar to the signs of dry eyes but remain for a certain period of time. These include decreased tear film stability till 3 months after PRK and LASIK,[142] and decreased tear secretions at 1 month after LASIK[142,143] and came back to the preoperative values

postoperatively after 6 months.[144] Comparison between LASIK and PRK showed that the tear secretion is highly decreased in LASIK when compared to PRK postoperatively 6 months,[145] while others report no significant change in tear secretions between PRK and LASIK at 1 month after refractive surgery.[146] Tear osmolarity was increased after LASIK and LASEK till 12 months postoperatively, but no difference in tear osmolarity between the two surgeries.[141] Tear meniscus height and tear thinning time were not affected in LASIK till 6 months.[147] These dry eye changes post-refractive surgery are transient lasting from a few weeks to months.[148] Corneal sensitivity was found to be reduced after laser refractive surgery because of the neurotrophic effect, where long-term corneal sensitivity is reduced in LASIK when compared to PRK and SMILE.[149–151]

1.3.3 Literature on changes in tear film after refractive surgery among pre-existing dry eyes

Apart from contact lens wear,[144] Asian race[139] and female gender,[136] pre-existing dry eye is one of the greatest risk factors for the development of severe dry eye after refractive surgery.[152] Studies have reported that dryness exists in patients presenting for refractive surgery, around 10-50%.[153,154] The prevalence of these dry eye symptoms before LASIK was reported between 38 and 75%.[155,156] In patients with preoperative dry eye (Schirmer's test <5mm or tear stability < 5sec in the presence of fluorescein corneal staining), the Schirmer's test and the tear break-up time were significantly lower, but the fluorescein scores were higher after till 1 year after LASIK.[152] Similarly, Tanbakouee E et al.[157] reported that tear secretions significantly deteriorated after PRK among those patients who had low Schirmer values preoperatively.

1.3.4 Literature on other side effects after laser refractive surgery

Among post-refractive surgery patients, apart from an increase in higher order aberrations[158] and glare,[159,160] it was found that the straylight values increased after surgery during the first two weeks after Photo Refractive Keratectomy (PRK). [161] Harrison JM et al. reported that these straylight values do not increase 1 month after PRK surgery.[162] Similarly, Beerthuizen JJ et al.[163] reported no changes in straylight values at 1 month post LASIK and PRK surgery. Contrary to this, it was found that intraocular stray light was reduced 15 days after LASIK surgery and returned to pre-op values at 6 months post LASIK surgery.[164] However, these straylight values were normal 1-year post-refractive surgery in wavefront guided-LASIK and PRK patients.[160]

Visual light sensitivity, also called photophobia, is also one of the side effects reported after laser refractive surgery. To study this, various questionnaires have been developed.[165–167] However, to monitor the progression of the disease, photosensitivity needs to be quantified. Several attempts have been made to quantify photophobia, however, it was difficult as their instruments were bulky and were not designed to use in a practical setting.[168–170] To overcome these disadvantages, Ocular Photosensitivity Analyser (OPA) was developed by the Bascom Palmer Eye Institute. The photosensitivity values measured using this instrument were found to be repeatable and reliable among healthy[171] and retinal pathology subjects.[172] Normative data was collected on healthy Indian emmetropes using an Ocular Photosensitivity Analyser.[173]

1.4 Gaps in the literature

Based on the above literature referred, a few gaps have been found in the published literature which include:

Objective-1: As presented in the literature review section, that studies have investigated the tear film and the MG morphology changes among dry eyes, diagnosed by the presence of both signs and symptoms. Few studies have examined these changes in subjects who report only symptoms with no signs. **However, there is not much information in the literature on tear film and MG morphology among subjects who have dry eye symptoms with no signs.**

Objective-2: Similarly, various studies have reported the incidence, prevalence, predictive factors and tear film changes among patients after laser refractive surgery. Also, tear film changes after laser refractive surgery among patients with pre-existing low tear stability and tear secretions were also studied. **But, among those subjects who report symptoms of dry eyes based on OSDI scores, the prevalence, predictive factors and tear film changes post laser refractive surgery are unknown.**

Objective-3: From the literature review presented for various functional changes after laser refractive surgery, it can be seen that many studies are reported on night vision disturbances, glare and intraocular light scattering. **However, photophobia which is a frequently observed symptom after laser refractive surgery is not studied.**

1.5 Addressing research gaps:

Objective-1: There is not much information on the tear film and MG among subjects who have dry eye symptoms with no signs. In this observational study, for assessing symptoms of dry eye, a standard OSDI questionnaire, with a threshold score of ≥ 13[6] was used to differentiate pre-clinical dry eye subjects and normals. Symptomatic subjects (with an OSDI score of ≥ 13) without demonstrable clinical signs are defined as having pre-clinical dry eye.

Objective-2: The predictive factors of developing symptomatic dry eyes and tear film changes among these subjects post-laser refractive surgery remain unexplored. As the consequences of laser refractive surgery can sometimes be quite intense, it is worthwhile to understand the tear film changes after laser refractive surgery among patients with pre-existing symptoms of dry eye and study the preoperative variables that lead to the development of symptomatic dry eyes.

Objective-3: Visual light sensitivity or photophobia is one of the most frequent symptoms often seen after refractive surgery, which has been overlooked. The current study rectifies these shortcomings by studying the visual light sensitivity after laser refractive surgery using an Ocular Photosensitivity Analyser (OPA).

1.6 Hypothesis:

Objective-1:

Null hypothesis: There are no tear film and MG morphology changes among subjects with pre-clinical dry eyes when compared to normals.

Alternate hypothesis: Tear film and MG morphology changes are seen in subjects with pre-clinical dry eyes when compared to normals.

Objective-2:

Null hypothesis: There is no effect of preoperative variables on changes in tear film after laser refractive surgery among symptomatic dry eyes. There are no changes in tear film after laser refractive surgery among symptomatic dry eyes.

Alternate hypothesis: There is an effect of preoperative variables on the changes in tear film after laser refractive surgery among symptomatic dry eyes. There are changes in tear film after laser refractive surgery among symptomatic dry eyes.

Objective-3:

Null hypothesis: There is no effect of laser refractive surgery on the change in visual light sensitivity measured as visual photosensitivity thresholds.

Alternate hypothesis: There is an effect of laser refractive surgery on the change in visual light sensitivity measured as visual photosensitivity thresholds.

1.7 Objectives:

Based on this background and review of literature, the following gaps have been addressed in this these by studying the three objectives.

Objective-1: Evaluate the changes in the tear film and meibomian gland (MG) morphology among subjects with pre-clinical dry eye and compare it with the normals defined by the Ocular Surface Disease Index score

Objective-2: Predictive Factors and early tear film changes of Symptomatic Dry eyes before and after Laser Refractive Surgery

Objective-3: Assessment of Visual Photosensitivity Thresholds after Laser Refractive Surgery using an automated Ocular Photosensitivity Analyser

Chapter-2:Changes in the Tear Film and Meibomian Gland Morphology between Pre-clinical dry eye and Normal subjects represented by Ocular Surface Disease Index scores

This chapter is published as original research in Experimental Eye Research in July 2022.

Fatima A, Vadla P, Konda N. Changes in the tear film and meibomian gland morphology between preclinical dry eye and normal subjects represented by ocular surface disease index scores. *Exp Eye Res.*:109188.

2.1 Introduction

The tear film is the eye's outermost structure that serves as a barrier between the corneal epithelium and the environment.[174] It functions as a single dynamic unit with different compartments.[74] The outermost lipid layer is derived from meibomian glands, which helps in spreading the tear film across the ocular surface, which in turn slows tear evaporation.[74] Middle aqueous layer is formed by the main lacrimal gland, the accessory glands of Krause and Wolfring [75] contribute a majority of the tear film. The inner mucin layer serves as an interface allowing the aqueous layer to adhere more easily.[175]

Any alteration in tear volume, composition, or thickness of these three layers causes disturbance to tear film, resulting in ocular surface dryness. This dryness leads to various symptoms such as ocular discomfort, visual disturbance, transient blurring of vision and pain.[2] It was reported that 15-30% of adults suffer from such symptoms, which are mostly associated with dry eye.[176] Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS) defined dry eye as *"A multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface"*.[2]

Various invasive and non-invasive diagnostic tests are available to detect and diagnose dry eye. [6] Invasive tests are traditionally used and have low reproducibility and high inter-observer repeatability[45] and may lead to ocular surface changes.[46] To overcome this, various non-invasive diagnostic imaging techniques[45,177] have been evolved to assess the affected layers of the tear film and meibomian glands, which helps in monitoring the disease.[45] Additionally, several questionnaires are available which are used to quantify dry

eye symptoms.[178] Amongst them, the Ocular Surface Disease Index (OSDI) questionnaire is commonly used.

Among these imaging devices, currently available hand-held devices are Polaris Tearscope (bon Optic, Lubeck, Germany) and EASYTEAR view+ (EASYTEAR S.R.L., Trento, Italy).[179] Polaris Tearscope measures interferometry for assessing the lipid layer pattern and tear BUT, whereas EASY TEAR view+ additionally has an infrared (IR) camera, which helps in assessing the meibomian glands also. Bandlitz et al.[180] measured the repeatability of non-invasive break-up time (NIBUT) using EASYTEAR view+ and compared it with commercially available devices (Polaris tearscope, Keeler tearscope and Keratograph 5M), and found that these values are repeatable. Another study[181] quantified the parameters of eyelid margin to measure the number of ridges needed to quantify the images for confocal microscopy compared with EASYTEAR view+.

Meibomian gland dysfunction (MGD) is one of the common reasons for the unstable tear film.[15] Vital signs for MGD are morphological changes,[121] which occur before the onset of symptoms.[101] These morphological changes include atrophy or loss, tortuosity, thickening, and shortening of the meibomian gland. Among healthy subjects, MG structure and function were found to decrease with an increase in age.[182,183] MG atrophy was commonly seen among patients presenting for refractive surgery.[126] It was also reported that the dry eye subjects showed a significant increase in MG loss, especially in the lower lid,[122] and this loss significantly correlated with tear film and dry eye symptoms.[123]

Tear film changes among dry eyes, diagnosed by the presence of both signs and symptoms are well known. Furthermore, meibomian gland alterations among evaporative dry eye patients were found to be higher, especially in the lower lid, when compared to normals without dry eye disease[124] and MG irregularity might predict the presence of MG

dysfunction, and effect on the tear film.[125] Among symptomatic dry eyes, the tear turnover rate was found to be lesser when compared to asymptomatic controls.[128] However, there is not much information on the tear film and MG among subjects who have dry eye symptoms with no signs. Hence, the current study aimed to evaluate the tear film and meibomian gland morphology using non-invasive techniques among subjects with pre-clinical dry eye in comparison with normals represented by the OSDI scores.

2.2 Methods and methodology:

2.2.1 Study Design:

This was a prospective cross-sectional study. A convenient sampling method was used.

2.2.2 Sample size:

A total of 150 subjects who visited the University of Hyderabad's Eye Clinic for regular eye examination were enrolled. The sample size was estimated based on the expected mean difference of 4.5 and standard deviation of 6.7 of ocular symptoms based on the OSDI scores[6] with an error rate of 0.05 and power of 0.8, which was found by 35 subjects.

2.2.3 Inclusion and exclusion criteria:

Subjects between 18 and 40 years, with no history of ocular dryness, surgery, or contact lens wear were included in the study. Subjects with ocular or systemic conditions which are known to cause dry eyes were excluded.

2.2.4 Ethics:

The study was approved by the Ethics Committee of the University of Hyderabad (UH/IEC/2019/148). All the procedures were conducted according to the Declaration

of Helsinki. Informed consent was signed by all the subjects before participating in the study.

2.2.5 Study procedure:

The tear film and meibomian gland assessment were performed using EASYTEAR view+ (EASYTEAR S.R.L., Trento, Italy) by a single examiner. This is a hand-held device, attached to the slit lamp imaging system, and the images were captured using the software. This instrument assesses six components: Interferometry for lipid layer pattern, anterior segment, lacrimal meniscus, meibography, NIBUT, and BUT. [184] All the following tests mentioned below were performed on both eyes of each subject on the same day in the given order. A time interval of 5-10 minutes was given between each test so that the test results were not affected.

2.2.5.1 Symptom assessment:

The Ocular Surface Disease Index (OSDI),[48] and the Computer Vision Syndrome (CVS-Q).[185] Questionnaires were administered using online Google forms. These two questionnaires were completed by all the subjects, and the scores were computed. The OSDI score was calculated on a scale of 0 to 100, with higher scores indicating more disability.[48] For CVS-Q, a score of 6 points or higher indicates computer vision syndrome.

2.2.5.2 Non-invasive tear film tests:

Non-invasive tear break-up time (NIBUT) was measured using the instrument's timer as the time between the blink and the first appearance of an irregularity in the grid **(*Figure 11*A)**. This procedure was repeated three times, and the average was taken as the NIBUT measurement. Then the lipid layer pattern was captured **(*Figure 11*B)**, identified, and

graded[97] as open meshwork, closed meshwork, wave, amorphous, and colour fringe, with open meshwork being the thinnest, and colour fringe being the thickest. The lower tear meniscus height (TMH) was imaged by focusing on the lower lid margin (***Figure 11*C**). Images were then extracted, and TMH was measured using ImageJ 1.53 image analysis software (National Institutes of Health, Bethesda, Maryland, USA)[186].

2.2.5.3 Meibography and assessment of meibomian glands:

Meibomian glands (MG) of both the upper and the lower lids were imaged **(*Figure 12*A, B)** using the EASYTEAR view+ device (EASYTEAR S.R.L., Trento, Italy) attached to a slit-lamp imaging system. For each subject, 3 images were captured using software connected to the EASYTEAR view+ device, and the best quality image was taken for analysis. These images were then extracted and analysed using ImageJ 1.53 image analysis software (National Institutes of Health, Bethesda, Maryland, USA)[186]. The variables assessed were MG length, width, loss, and tortuosity. For better visibility of MGs, an enhanced local contrast option in Image J was used.[121]

The length and width of MG were measured from the central three glands for each eyelid. A known size of an image in mm was used to measure the length and the width of MG using ImageJ software. MG length was measured using the segmented line tool, tracing the length of each MG from the upper border of the tarsal plate to the complete length of MG (***Figure 12*C**, refer L). The MG width was measured using a straight-line tool as the horizontal distance from one end to the other end of each meibomian gland (***Figure 12*C**, refer W). For MG loss, the tarsal area was outlined with a polygon function, and the total meibomian gland area was measured. Then, the MG loss area was outlined using a freehand tool and measured (***Figure 12*C**, refer LOSS). The formula[187] was used to calculate the MG

loss in percentage. This MG loss was measured objectively by two masked examiners. This MG loss was also graded using meiboscale[104] as grade 0 with no gland atrophy, grade 1 indicating ≤25% gland atrophy, grade 2 indicating 26% to 50% gland atrophy, grade 3 indicating 51% to 75% gland atrophy, and grade 4 indicating ≥75% gland atrophy. MG tortuosity was defined as the MG gland being distorted more than 45 degrees.[188] This was analysed using ImageJ (***Figure 12*C**, refer TT), where the angle of the distorted glands was measured, and all the glands with an angle greater than 45 degrees were counted manually for the same eyelid.[121] This was then graded using a 3-point scale,[188] where grade 0 indicates no distortion, grade 1 indicates 1 to 4 distorted glands, and grade 2 indicates five or more distorted glands.

2.2.5.4 Invasive tear film tests:

Schirmer's test I was performed by placing the Schirmer's paper strip in the temporal one-third of the lower eyelid margin without touching the cornea, and the score was measured based on the length of wettability of the strip after a period of 5 minutes.[6] The corneal staining was assessed using a slit lamp biomicroscope after the instillation of commercially available sterile fluorescein paper strips (Fluoro Touch, Madhu Instruments Pvt. Ltd., New Delhi, India). Corneal staining was graded using the Efron grading scale,[189] where grade 0 indicates normal, grade 1 indicates trace staining, grade 2 indicates mild staining, grade 3 indicates moderate staining, and grade 4 indicates severe staining.

2.2.6 Statistical analysis:

Statistical analysis was performed using SPSS software Version 25 (SPSS Inc., Chicago, USA). Normality was analyzed using the Kolmogorov-Smirnov test. Correlations between the variables were assessed using Spearman's rank correlation. Agreement between two examiners was analyzed using Intraclass correlation (ICC) and Friedman's chi-square test. The subjects were differentiated into two groups based on the OSDI threshold score of 13.[6] Symptomatic subjects (with OSDI score ≥ 13) without demonstrable clinical signs were categorized as pre-clinical dry eye,[2] whereas subjects without symptoms (OSDI score < 13) were grouped as normals. Comparisons between the two groups were performed using the Mann-Whitney U test. The significance value was set at 0.05.

Figure 11: Tear film imaged using EASYTEAR view+. (A) Non-invasive breakup time showing the irregularity in the grid (B) Amorphous pattern of the lipid layer thickness. (C) Lower tear meniscus height (TMH) measured using Image J software

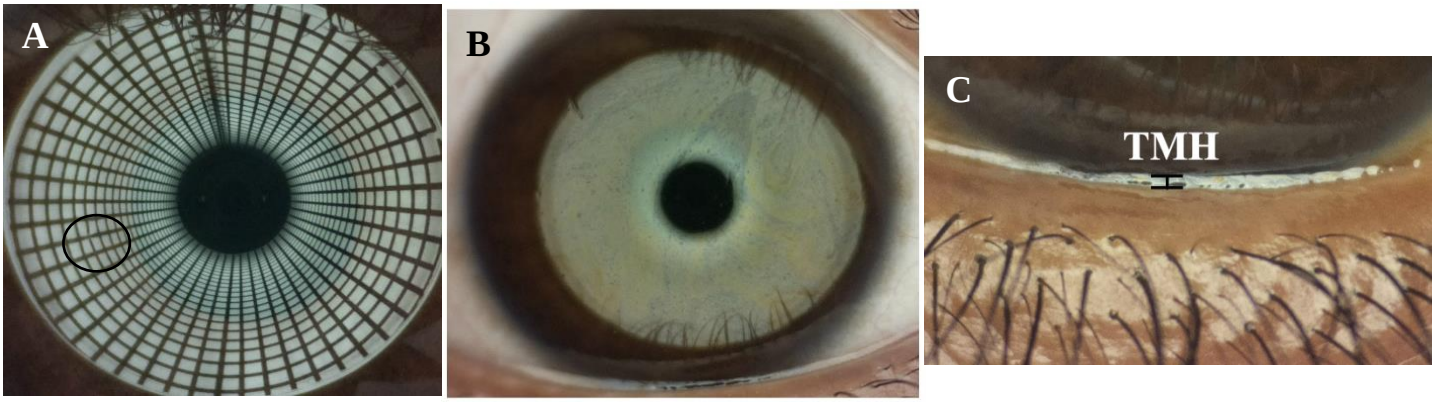
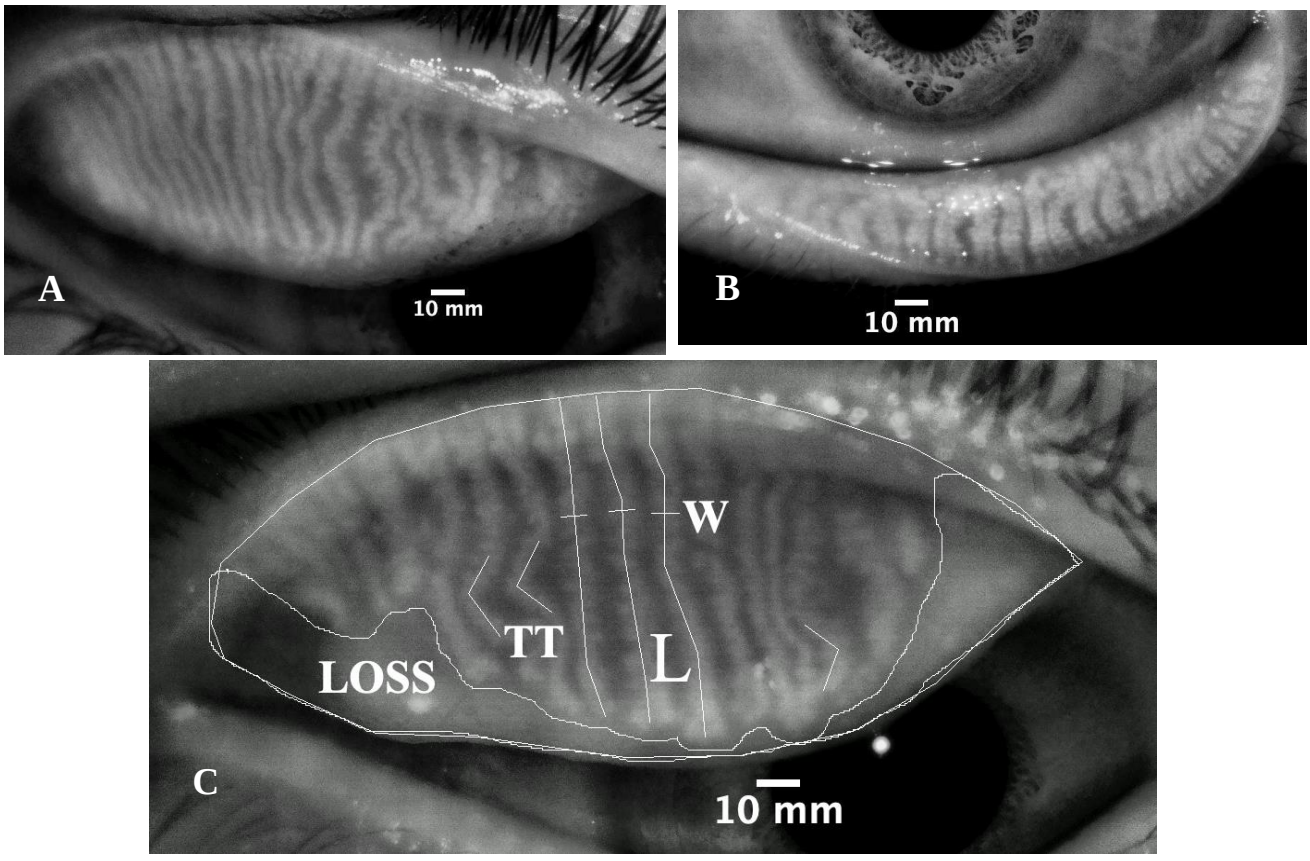


Figure 12: Meibomian gland images of (A) Upper lid and (B) Lower lid. (C) Meibomian gland (MG) morphology measurements showing MG length (L), MG width (W), MG loss (LOSS), and MG tortuosity (TT), measured using Image J software. The contrast is enhanced using Image J software for better visualisation of MG.



2.3 Results:

Data from 149 subjects were included for analysis, and one subject was excluded as the quality of the images captured was not good. Due to the significant correlations between the eyes ($r \geq 0.60$, $p<0.0001$), right eye measurements for all the subjects were considered for analysis. ***Table 3*** shows the demographic details for the subjects along with OSDI and CVS-Q scores. Overall, none of the subjects had grade-3 or grade-4 loss on meiboscale **(Figure *13*A, B)**, however, these subjects were distributed among all tortuosity scores **(Figure *14*C, D)** for the upper and the lower lid. A significant moderate positive correlation was found between OSDI and CVS-Q scores ($r=0.66$, $p<0.001$,**Figure *15*).**

Table 3: Descriptive statistics of the study variables.

Median (IQR)	**All (n=149)**	**Normals (n=84)**	**Pre-clinical dry eye (n=65)**
Age	22.00 (21.00 - 23.00)	22.00 (20.25 - 23.75)	22.00 (21.00 – 23.00)
Male: Female	78:71	47:37	29:36
OSDI Score, grade	10.41 (4.16 - 18.75)	6.25 (2.08 – 8.33)	20.83 (16.66 - 29.16)
CVS-Q Score, grade	5.00 (2.00 - 9.00)	3.00 (2.00 – 6.00)	8.00 (6.00 - 12.00)

OSDI, Ocular Surface Disease Index; CVS-Q, Computer Vision Syndrome Questionnaire; IQR, Interquartile range.

Figure 13: Pie chart showing the distribution of meiboscale for MG loss for the upper (A) and lower lid (B)

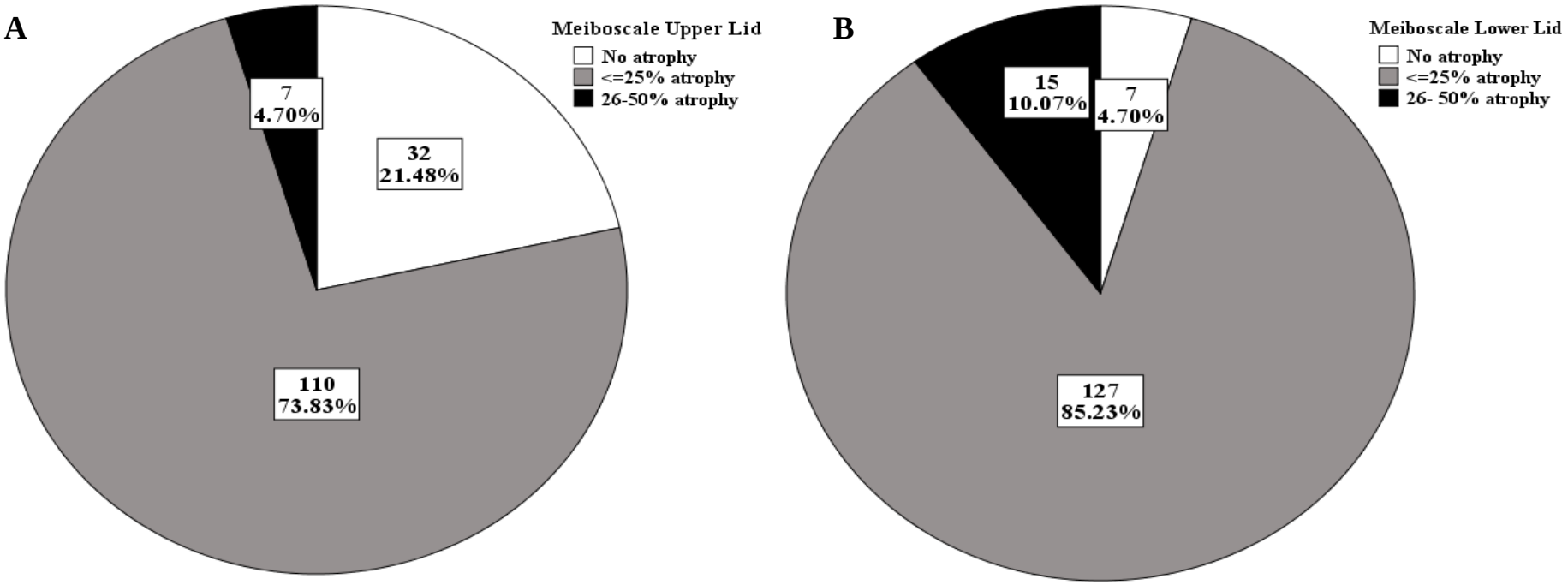


Figure 14: Pie chart showing the distribution of tortuosity score for the upper lid (C) and lower lid (D) among the subjects.

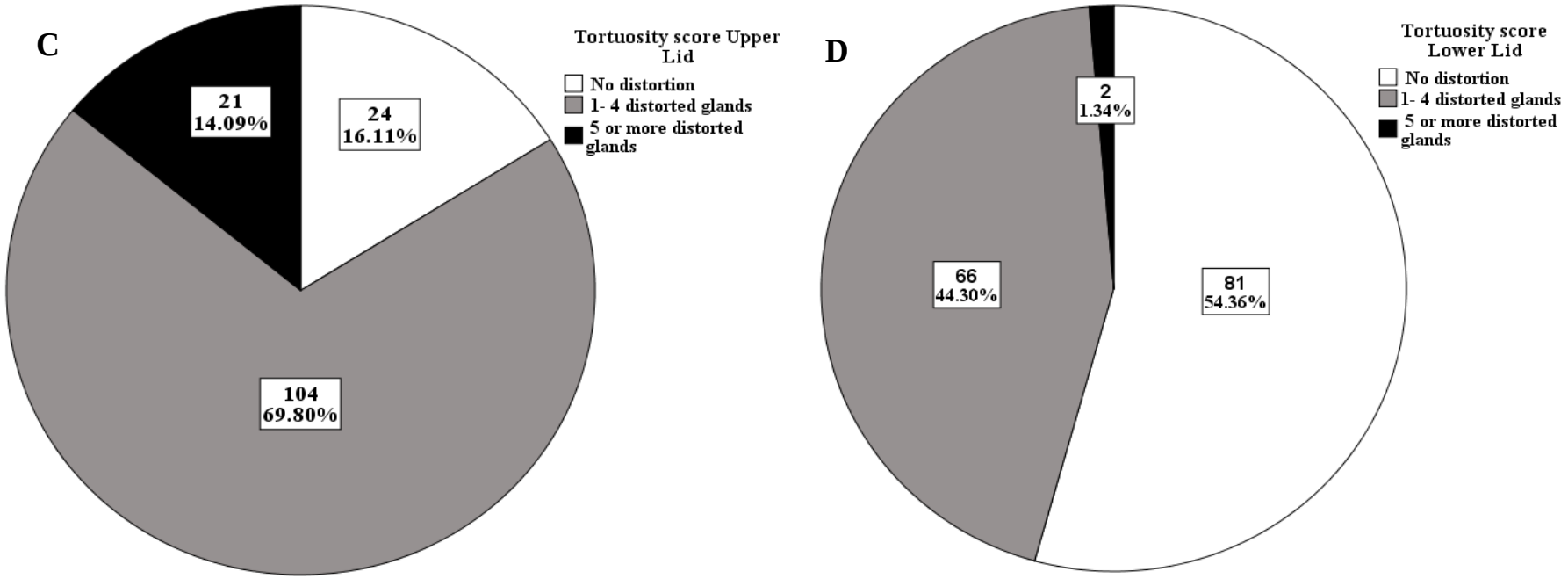
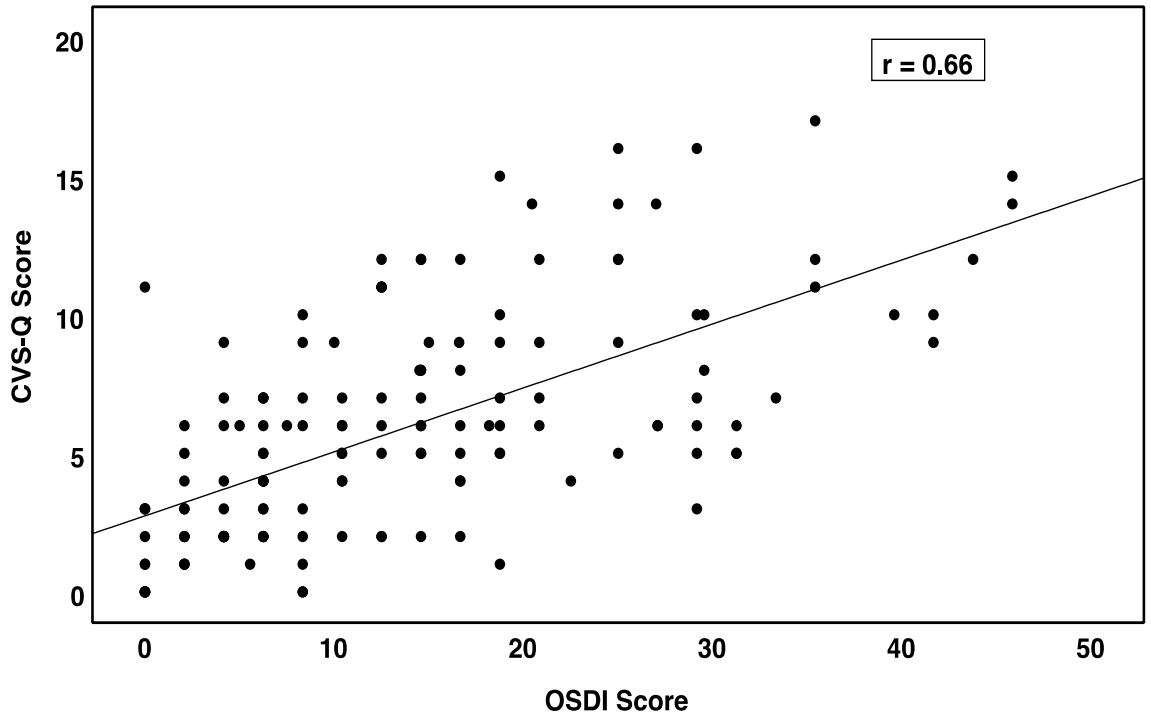


Figure 15: Correlation between Ocular Surface Disease Index (OSDI) score and Computer Vision Syndrome Questionnaire (CVS-Q) score.



2.3.1 Comparison of the tear film and MG morphology between pre-clinical dry eye and normals:

Sixty-five subjects had OSDI threshold scores of ≥ 13 and were grouped into the pre-clinical dry eye, whereas 84 subjects with OSDI scores < 13 were grouped as normals **(*Table 3*)**. CVS-Q scores were higher in the pre-clinical dry eye group in comparison with the normal, and this difference was statistically significant (Z=-6.72, p<0.0001).

2.3.1.1 Comparison of the tear film between pre-clinical dry eye and normals:

NIBUT was lower among subjects with pre-clinical dry eye when compared to normals (Z=-2.13, p=0.03), which was statistically significant. TMH, although lower in the pre-clinical dry eye group than normals, did not show any statistical significance (Z=-1.63, p=0.10). Schirmer's test values were similar in both groups (Z=-0.72, p=0.46). There was no significant difference in corneal staining between the groups (Z=-0.18, p=0.85) (***Table 4***).

Table 4: Comparison of the tear film tests between pre-clinical dry eye and normals.

Median (IQR)	**Pre-clinical dry eye**	**Normals**	**p value**
NIBUT, sec	9 (8 - 10)	10 (8 - 11)	**0.03**
TMH, mm	0.26 (0.21 - 0.31)	0.27 (0.22 – 0.31)	0.10
Schirmer's test, mm	25 (19 - 32.25)	25 (20 - 35)	0.46
Corneal staining, grade	0 (0 - 0)	0 (0 - 0)	0.85

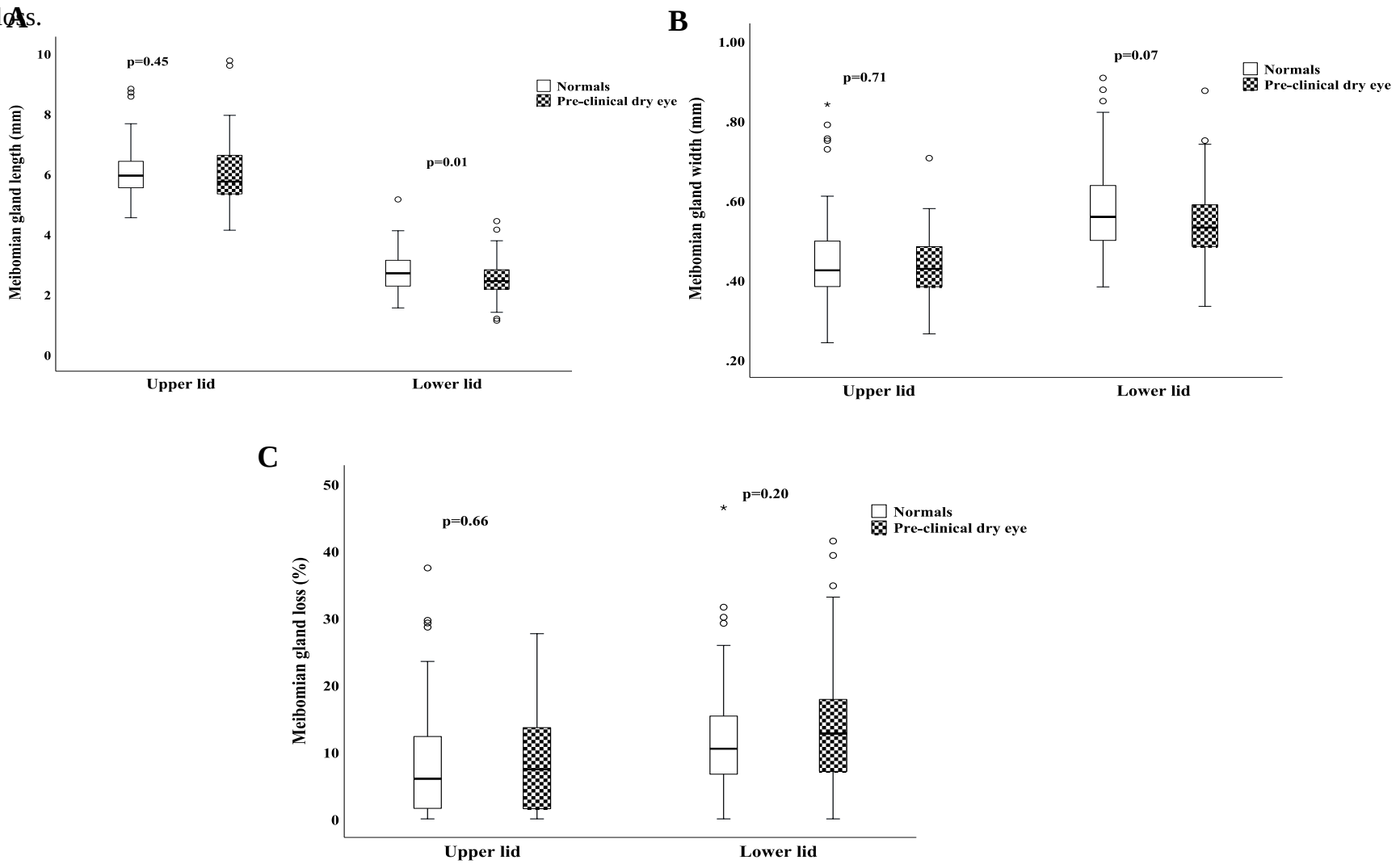
NIBUT, Non-Invasive Break-up Time; TMH, Tear Meniscus Height; IQR, Interquartile range.

2.3.1.2 Comparison of MG morphology between pre-clinical dry eye and normals:

MG loss for both the upper and the lower lid was measured objectively and graded by two examiners individually to assess the agreement. Good agreement between two examiners was found for MG loss grading for both the upper (ICC=0.79, Chi-square=1.48, p=0.223), and the lower lid (ICC= 0.78, Chi-square=1.05, p=0.304).

The MG length was reduced among subjects with pre-clinical dry eye for both the upper (Z=-0.75, p=0.45) and the lower lids (Z=-2.58, p=0.01), this was statistically significant for the lower lid only (**Figure *16*A**). The MG width was lesser for the upper (Z=-0.36, p=0.71) and the lower lids (Z=-1.79, p=0.07) in the pre-clinical dry eye group, where no significant differences were found for both the lids **(Figure *16*B)**. The MG loss for the upper lid was higher among subjects with pre-clinical dry eye when compared to normals (Z=-0.43, p=0.66), and the lower lid (Z=-1.28, p=0.20), did not show any statistical significance (**Figure *16*C**). Similarly, the tortuosity score for the upper and the lower lid was not significantly different between the groups (upper lid: Z=-1.10, p=0.27; lower lid: Z=-0.12, p=0.89).

Figure 16: Comparison of meibomian gland length, width and loss between pre-clinical dry eye and normals. Normal and pre-clinical dry eye groups are shown in plain and patterned box plots respectively. (A) Meibomian gland length (B) Meibomian gland width (C) Meibomian gland loss.



2.3.2 Relationship between computer vision syndrome questionnaire (CVS-Q) with tear film and meibomian gland morphology:

Subjects were divided into two groups based on the CVS-Q cutoff score of 6[185]. A CVS-Q score of greater than 6 indicates computer vision syndrome. In the current study, seventy-five subjects had a CVS-Q score < 6 (median= 2, IQR= 2 to 4), and 74 had a CVS-Q score >6 (median= 9, IQR= 6.25 to 11.00). Comparisons using the Mann-Whitney U test showed statistically significant differences for OSDI score (Z=-6.43, p=0.0001), TMH (Z=-2.05, p=0.04), and MG length of the lower lid (Z=-2.13, p=0.03). The other variables did not show statistical significance (all p>0.05, ***Table 5***).

Table 5: Comparison of the tear film and MG parameters by CVS-Q cut-off score grouping.

Median (IQR)		**CVS-Q -**	**CVS-Q+**	**p value**
OSDI score, grade		6.25 (2.08-11.45)	16.66 (10.93 -27.06)	**0.0001**
NIBUT, sec		9.00 (8.00-11.00)	10.00 (8.00-11.00)	0.293
TMH, mm		0.28 (0.23-0.31)	0.26 (0.21 – 0.31)	**0.040**
Schirmer's test, mm		25.00 (19.00-35.00)	25.00 (20.00-34.75)	0.886
Corneal staining, grade		0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.992
MG length, mm	**UL**	5.89 (5.56 – 6.52)	5.93 (5.29-6.58)	0.624
	LL	2.69 (2.36 – 3.08)	2.41 (2.18-2.83)	**0.033**
MG width, mm	**UL**	0.42 (0.38-0.48)	0.43 (0.39-0.48)	0.441
	LL	0.55 (0.50-0.60)	0.53 (0.48-0.60)	0.296
MG loss, %	**UL**	5.96 (1.96-13.61)	7.42 (1.50-13.07)	0.900
	LL	9.58 (6.07-15.34)	12.74 (7.68-17.01)	0.118
Tortuosity	**UL**	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.452
score, grade	**LL**	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.941

OSDI, Ocular surface Disease Index (OSDI); NIBUT, Non-Invasive Break-up Time; TMH, Tear Meniscus Height; MG, Meibomian Gland; UL, Upper Lid; LL, Lower Lid, CVS-Q-, Computer Vision Syndrome Questionnaire negative; CVS-Q+, Computer Vision Syndrome Questionnaire positive, IQR, Interquartile range.

2.4 Discussion:

This study assessed the changes in the tear film and MG morphology among pre-clinical dry eye and normal subjects based on the OSDI threshold score. Among all the subjects, the overall MG loss was found to be lower. Interestingly, it was found that 65 (43.6%) subjects had pre-clinical dry eye, and the rest 84 were normals. Among subjects with pre-clinical dry eye, a significant reduction in NIBUT, and MG length of the lower lid were found. However, other variables such as TMH, Schirmer's test, corneal staining, MG width, loss, and tortuosity scores did not significantly differ from normals. Similarly, 74 (49.6%) of the subjects in this study had computer vision syndrome graded using CVS-Q. Among these subjects, OSDI scores were found significantly higher, along with a reduction in the TMH and MG length of the lower lid.

NIBUT was found to be lower in the subjects studied when compared to normative data reported in the literature.[190,191] A study[192] reported that the Indian population has a shorter break-up time when compared to other populations. The mean length and width of MGs of both the upper and the lower eyelids were comparable to the reported literature.[125,193] Minimal MG loss for both the upper and the lower lid was found in this study, compared to the other studies which reported MG loss.[121,123] This might be due to the difference in the age group included in these two studies.[122] It was reported that the meiboscale is lesser in younger than older sub-groups.[126,127] The tortuosity score found in this study was similar to what has been published.[126] This suggests that among MG morphology, MG loss was minimal among young subjects. Whereas the other MGs morphological changes remain similar as reported in the literature.

In the present study, the subjects were differentiated into two groups based on the OSDI threshold score as pre-clinical dry eye group and normals, where NIBUT was found lower in the pre-clinical dry eye group when compared to normals. Similarly, TBUT was found to be lower in a mildly symptomatic group compared to normals.[194] A recent study reported that fluorescein BUT was a sensitive indicator for differentiating pre-clinical dry eye from normals.[130] TMH and Schirmer's values were similar in the pre-clinical dry eye group and normals, with no statistical significance. Most of the studies also reported no correlations between OSDI and Schirmer's test,[195,196] indicating that it is not appropriate for diagnosing dry eye. These results indicate that among all tear film tests, NIBUT is most crucial in diagnosing pre-clinical dry eye.

In this study, MG loss was graded objectively, as it is more precise than subjective grading.[104] Due to variability in outlining the total MG area and loss area, MG loss was measured by two masked examiners, where good agreement was found between two examiners indicating good inter-observer variability, similar to what has been reported previously.[187]

In the pre-clinical dry eye group, it was seen that the length of the lower MG was significantly reduced when compared to normals. It was reported that among evaporative dry eye patients, MG was shortened when compared to healthy controls.[124] In this study, the MG width did not vary significantly between the groups. Similarly, among dry eye patients, no specific thickening or thinning of MG was found when compared to normals.[124] MG loss for the upper and the lower lid is found to be slightly higher in the pre-clinical dry eye group, with no significant difference. However, a study[197] reported significant MG loss in dry eye patients compared to healthy subjects. No significant differences were found in this study, as

the reported threshold value of MG loss to differentiate between OSDI+ and OSDI- groups was 16.9% at the upper lid and 28.7% at the lower lid respectively.[123] Tortuosity score, although higher in the pre-clinical dry eye group for the lower lid, did not show any statistical significance. Among evaporative dry eye patients, distorted glands were higher but no statistical significance was seen when compared to that of non-dry eye patients.[124] But, subjects with MGD had higher tortuosity when compared to normals.[198] These results suggest that among subjects with pre-clinical dry eye, there is a significant reduction in MG length of lower lid than normals as reported in dry eyes, but the MG loss and tortuosity were not significantly higher.

The use of a computer or visual display unit is one of the risk factors for dry eye.[8] Close to 50% of subjects in the current study were reported to have CVS. The study variables were assessed using CVS-Q. Subjects were divided into two groups based on cut-off score, where CVS-Q+ subjects had higher OSDI scores, similar to what has been found in the literature,[199,200] where higher OSDI scores were found for subjects using computers and smartphones. In the CVS-Q+ group, TMH was significantly lower than CVS-Q- group, similar to published articles,[200–203] where tear meniscus height was found to be reduced with computer use. In the previous literature,[200,203] subjects were grouped based on hours of computer use, whereas in this study, a questionnaire was used which detected the computer vision syndrome based on symptoms, its intensity, and frequency.

2.5 Limitations:

This study did not assess the functional changes such as meibum quality, gland expression, lid margin irregularity, and telangiectasia. Furthermore, studying these changes with MG morphology would provide a better understanding of different grades of MGD and its association with dry eye. In future studies, it is recommended to assess the tear film between VDT and non-VDT users using the standard questionnaire.

2.6 Conclusion:

In conclusion, this study compared the tear film and MG morphology of both the upper and the lower lids between the pre-clinical dry eye and normals grouped based on their OSDI scores. Most of the subjects who presented for a regular eye examination had a pre-clinical dry eye defined by their OSDI scores. Lower NIBUT in the pre-clinical dry eye group indicates positive diagnostic tear film tests to differentiate from normals. TMH, Schirmer's test, and corneal staining play no significant role. A decrease in the MG length of the lower lid may indicate early signs of dry eye disease among subjects with pre-clinical dry eye. Nearly half of the current study (49.6%) subjects presented for regular eye examination were found to have computer vision syndrome and had significant high OSDI scores, lower TMH and MG length in the lower lid. This study's results indicate that the majority of the young individuals presenting for the regular eye examination may have pre-clinical dry eye. Hence, it is important to administer the OSDI questionnaire and perform non-invasive tests such as NIBUT and IR imaging of MG as routine tests to detect pre-clinical dry eye.

Chapter-3: Predictive Factors and early Tear Film changes of Symptomatic Dry Eyes after Laser Refractive Surgery

3.1 Introduction:

Dry eye is defined as[2] *"A multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".* There are various risk factors that cause dry eye, among which laser refractive surgery is one of them.[8] It is widely performed globally to correct the eye's refractive error. Within laser refractive surgery procedures, the most commonly performed ones include Photo Refractive Keratectomy (PRK) and Laser Insitu Keratomileusis (LASIK). Although these procedures are evolving in the current era, some of the side effects are still seen amongst which dry eye is the most common.[115] It was reported that the prevalence of dry eye after refractive surgery varies between 40 and 59% at 1 month; 10 and 40% at 6 months post-surgery.[134,135]

The most common aetiology behind the development of dry eye after PRK is the damage to the sub-basal nerve plexus and the nerve endings.[138] Whereas in LASIK, the deeper corneal nerves are damaged during flap creation. In SMILE, the vertical side cut is smaller, leading to less damage to the corneal nerves. It was found that 95% of patients report at least one dry-eye-related symptom immediately following LASIK surgery.[133] However, these symptoms tend to recede with time. In the early postoperative period, these symptoms are higher in PRK due to discomfort caused by the healing epithelium.[204] Between LASIK and PRK, the incidence of dry eye symptoms was reported as similar after the initial healing period.[205]

Various studies have reported the clinical signs of dry eye after laser refractive surgery. Where studies have reported decreased tear film stability till 3 months after PRK and LASIK,[142] and decreased tear secretions at 1 month after LASIK[142,143] and came back to normal at 6 months after LASIK.[144] Comparison between LASIK and PRK showed that the

tear secretion is highly decreased in LASIK when compared to PRK postoperatively 6 months,[145] while others report no significant change in tear secretions between PRK and LASIK at 1 month after refractive surgery.[146] Tear meniscus height and tear thinning time were not affected in LASIK till 6 months.[147] These dry eye changes post-refractive surgery are transient and last for a few weeks to months.[148]

Chronic dry eye is characterised by the presence of dry eye symptoms or signs lasting beyond 6 months after refractive surgery. The reported incidence of chronic dry eye symptoms varied between 20% and 55%.[40,136,137] Bower et al.[138] found the incidence of chronic dry eye disease (based on signs and symptoms) after LASIK and PRK as 5% and 0.8% respectively. This is based on signs and symptoms that developed chronic dry eye 1-year post-refractive surgery. Furthermore, it was reported that preoperative low values on Schirmer's test increase the risk for the development of chronic dry eye disease in PRK and LASIK.[138,140]

Also, it is not surprising to find dry eye symptoms existing among patients presenting for refractive surgery.[206] Wherein, the prevalence of these pre-existing dry eye symptoms was 38-75%.[155,156] It was found that pre-existing dry eye is a significant risk factor for the development of chronic dry eye after LASIK.[152] Among patients with the preoperative dry eye; Schirmer's test and the tear break-up time were significantly lower, whereas fluorescein scores were higher after LASIK.[152] Similarly, tear secretions were significantly worsened after PRK in patients with low Schirmer values preoperatively.[157] Among those with dry eye symptoms prior to surgery, the transient changes in the signs of dry eyes are not investigated. Hence, this study aimed to assess the 1) Predictive factors for the development of transient or persistent symptomatic dry eyes after laser refractive surgery and 2) Tear film changes among the symptomatic dry eye group.

3.2 Methods and methodology:

3.2.1 Study Design:

This was a prospective case-control study conducted at LV Prasad Eye Institute, Hyderabad, India.

3.2.2 Sample size:

Seventy-one subjects were recruited for this study. The sample size was calculated based on a previous study where it was reported that 72% of the patients with pre-existing dry eyes have dry eyes after refractive surgery,[152] with unmatched cases and controls (1:3) with a power of 0.8 and an error rate of 0.05 and was estimated as 15 cases and 45 controls.

3.2.3 Inclusion and exclusion criteria:

Inclusion criteria included subjects suitable for laser refractive surgery after their comprehensive eye examination, with no history of ocular dryness or surgery, and other systemic conditions which lead to dry eyes.

3.2.4 Ethics:

The study was approved by the Institutional Ethics Committee of LV Prasad Eye Institute (LEC 03-19-232) and the University of Hyderabad (UH/IEC/2019/148). All the procedures were performed according to the tenets of the Declaration of Helsinki. Informed consent was signed by all the subjects before participating in the study.

3.2.5 Preliminary examination:

All the subjects had a comprehensive preoperative eye examination; which includes: ocular and systemic history, uncorrected and corrected distance visual acuity (UDVA, CDVA) manifest retinoscopy, subjective acceptance, slit-lamp biomicroscopic examination, dilated examination of posterior segment, intraocular pressure measurement, computerized assessment of corneal topography and thickness using Oculus Pentacam. Then the subjects were scheduled for laser refractive surgery.

3.2.6: Study procedure:

For the study purpose, the subjects filled out the Ocular Surface Disease Index (OSDI) questionnaire followed by an evaluation of the following dry eye tests. All the dry eye tests along with the OSDI questionnaire were assessed preoperatively on the day of surgery and post-operatively 1 week after laser refractive surgery.

3.2.6.1 Ocular Surface Disease Index (OSDI) questionnaire: This is a 12-item questionnaire that assesses dry eye symptoms and effects on vision-related function in the past week of the patient's life.[207] The final score varies between 0 and 100. Higher scores indicate increased severity of dry eye.

3.2.6.2 Non-invasive breakup time (NIBUT): NIBUT was measured using EASYTEARview+, as the time from the initial blink to the appearance of the irregularity in the illuminated grid. An average of three measurements were taken as final NIBUT.

3.2.6.3 Tear meniscus height (TMH): Lower TMH was captured using EASYTEARview+ software. Images were then retrieved and tear meniscus height was measured in mm using ImageJ 1.53 image analysis software (National Institutes of Health, Bethesda, Maryland, USA).[186]

3.2.6.4 Schirmer's test: Schirmer's test was performed by placing the paper strips in the lower tarsal conjunctiva at temporal one-third to avoid touching the cornea. The wettability of the strip in mm in 5 minutes is documented.[6]

3.2.7 Predictors for transient and persistent symptomatic dry eyes:

Preoperative findings of tear film variables such as NIBUT, TMH and Schirmer's tests were selected as predictors of transient and persistent symptomatic dry eye after laser

refractive surgery. Other preoperative variables selected as predictive factors include spherical equivalent error, corneal thickness, and mean keratometry.

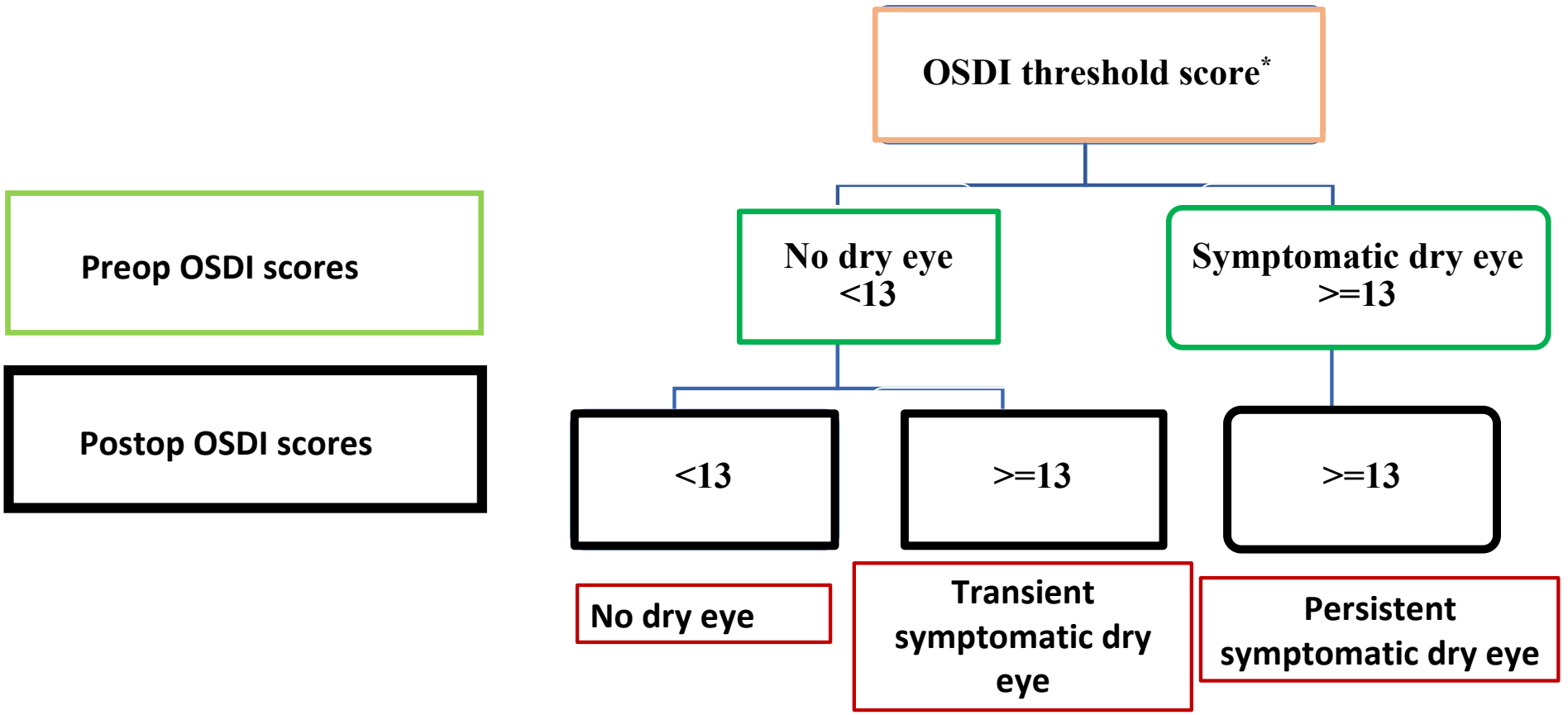
A single surgeon performed laser refractive surgery on all the patients, and the procedure was uneventful.

3.2.6 Symptomatic Dry eye classification:

In this study, symptomatic dry eye subjects are categorised based on the symptoms reported on OSDI scores both pre and postoperatively. The OSDI threshold value of ≥13 was used to differentiate symptomatic dry eye subjects from normals.[2] The subjects were divided into three groups based on their preoperative and postoperative scores at the conclusion of the study (**Figure *17***).

No dry eye group: Subjects who do not have any symptoms (OSDI scores <13) before and after laser refractive surgery, 2) **Transient dry eye group:** Subjects who did not have any symptoms preoperatively (OSDI scores <13) but developed symptomatic dry eyes postoperatively (OSDI scores ≥13), 3) **Persistent dry eye group:** Subjects who had symptoms (OSDI scores ≥13) both pre and postoperatively.

Figure 17: Classification of dry eye groups based on the OSDI scores at the preoperative and postoperative visits.



3.2.8 Statistical analysis:

Data was analyzed using SPSS software Version 25 (SPSS Inc., Chicago, USA). Normality was analyzed using the Kolmogorov-Smirnov test. Linear regression was performed to predict the changes in the independent variables and the development of persistent or transient symptomatic dry eye. Comparisons between preoperative and postoperative visits were performed using Wilcoxon signed rank test. Comparisons between the dry eye groups were performed using the Kruskal Wallis test. Significant comparisons were then analyzed using the Mann-Whitney U test, where the significance values were adjusted using Bonferroni correction. The statistical significance value was set at 0.05.

3.3 Results:

The Median (IQR) age of the subjects was 24 (22-27) years. 34 (47.8%) subjects were males and 37 (52.1%) were females.**Table *6*** shows the descriptive statistics for the preoperative variables. 10 (14%) subjects lost to follow-up at the postoperative visit. Among 71 subjects, 50 (70.4%) underwent PRK surgery and 21(29.5%) subjects underwent LASIK surgery.

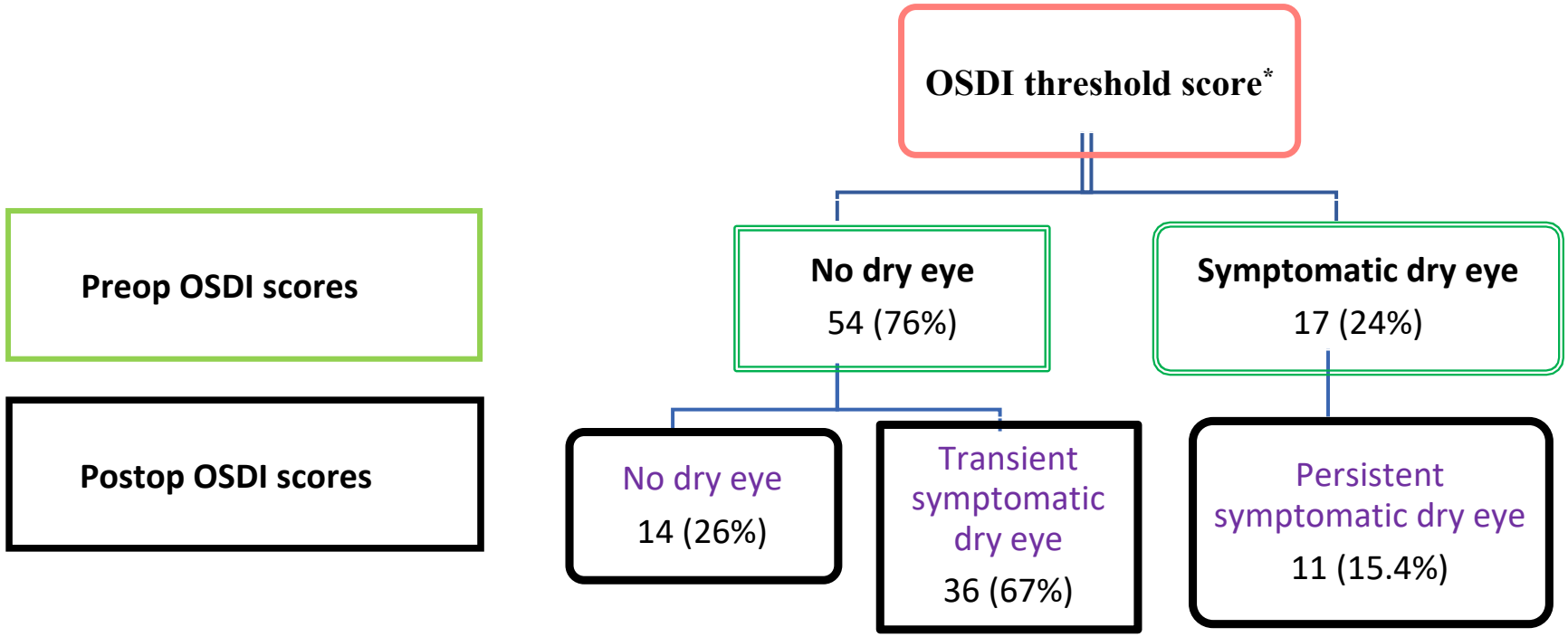
Table 6: Descriptive statistics of all the subjects at the preoperative visit.

Variable	**Median (IQR)**
Spherical equivalent error, D	-5.37 (-6.75 to -2.75)
Corneal thickness, μm	517 (495-542)
Mean keratometry, D	44 (43.15 - 45.1)
OSDI score, score	6.18 (0 - 12.5)
Non-invasive breakup time	12 (9-16)
Tear meniscus height	30 (18-32)
Schirmer's test	0.21 (0.16 - 0.24)

3.3.1 Predictive factors for symptomatic dry eyes:

Among all the subjects, 17 (23.9%) of them had a symptomatic eye. **Figure *18*** shows the distribution of subjects in the three groups. 4 subjects lost follow-up in the no dry eye group, whereas 6 subjects lost follow-up in the symptomatic dry eye group.

Figure 18: Distribution of subjects in dry eye groups based on the threshold OSDI score



Linear regression showed that the selected preoperative variables accounted significantly for the occurrence of transient symptomatic dry eye (R square=0.408, F=4.22, p=0.001) and persistent symptomatic dry eye (R square=0.912, F=23.76, p=0.0001). Among the selected variables, preoperative OSDI scores and NIBUT were statistically significant predictors for development of the transient symptomatic dry eye (**Table *7***), whereas preoperative OSDI scores and Schirmer's test were statistically significant predictors for development of the persistent symptomatic dry eye (**Table *8***).

Table 7: Predictive modelling for the occurrence of transient symptomatic dry eye after laser refractive surgery

Independent variable	**P value**	**R square**
Constant	0.011	0.408 (F=4.22, P=0.001)
Preop spherical equivalent error	0.499	
Preop corneal thickness	0.133	
Mean-K	0.004	
Preop OSDI	**0.001**	
Preop NIBUT	**0.006**	
Preop TMH	0.928	
Preop Schirmer's test	0.823	

Table 8: Predictive modelling for the occurrence of persistent symptomatic dry eye after laser refractive surgery

Independent variable	P value	R square
Constant	0.250	0.912 (F=23.76, **P=0.0001)**
Preop spherical equivalent error	0.340	
Preop corneal thickness	0.773	
Mean-K	0.107	
Preop OSDI	**0.0001**	
Preop NIBUT	0.803	
Preop TMH	0.871	
Preop Schirmer's	**0.035**	

3.3.2 Comparison of tear film tests between preoperative and postoperative visits:

Among all the subjects, there was a significant increase in the OSDI scores at the postoperative visit (Z=6.68, p=0.0001). Similarly, NIBUT (Z=-6.22, p=0.0001), TMH (Z=-2.77, p=0.006) and Schirmer's test values (Z= -3.40, p=0.001) were significantly reduced at the postoperative visit (**Table *9***).

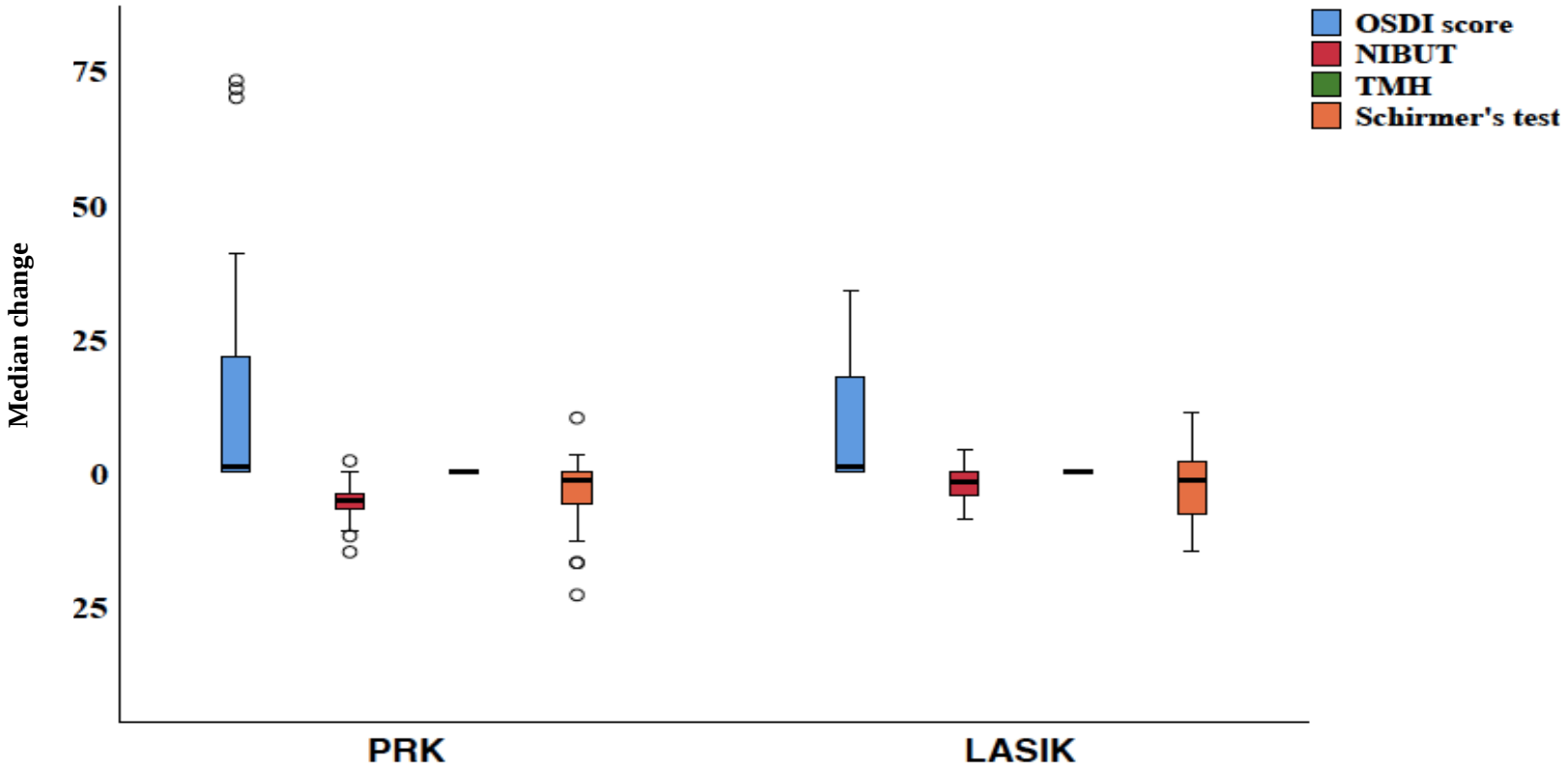
Table 9: Comparison of tear films tests between pre and postoperative visit

Variable	Median (IQR)	p value
Preop OSDI score	6.18 (0 – 12.5)	**0.0001**
Postop OSDI score	29.16 (16.67 – 40.62)	
Preop NIBUT	12 (9-16)	**0.0001**
Postop NIBUT	6 (4-11)	
Preop TMH	0.21 (0.16 – 0.24)	**0.005**
Postop TMH	0.19 (0.14 – 0.22)	
Preop Schirmer's test	30 (18 – 32)	**0.001**
Postop Schirmer's test	25 (15 – 30)	

3.3.3 Comparison of change in tear film tests between preoperative and postoperative visits among PRK and LASIK:

Among all the tear film tests, the change in NIBUT from preoperative to postoperative visit was significantly higher after PRK when compared to LASIK (Z=-3.22, p=0.001). Other variables did not show any statistically significant change between PRK and LASIK (p>0.05, **Figure *19***)

Figure 19: Changes in tear film tests at postoperative visit between PRK and LASIK groups.



3.3.4 Comparison of tear film between the dry eye groups:

OSDI scores at the preoperative visit were significantly different between the dry eye groups (Kruskal Wallis H=15.43, p=0.0001). On post hoc comparisons, statistically significant higher scores were found in the persistent symptomatic dry eye when compared to the no dry eye (Z= -3.91, p=0.0001) and the transient symptomatic dry eye group (Z=-2.97, p=0.009). Similarly, at the postoperative visit, OSDI scores were significantly different between the groups (Kruskal Wallis H=18.07, p=0.0001). Post hoc tests showed significantly higher scores in the transient symptomatic dry eye group (Z=-3.78, p=0.0001) and the persistent symptomatic dry eye group (Z=-3.61, p = 0.001) when compared to the no dry eye (**Figure** A).

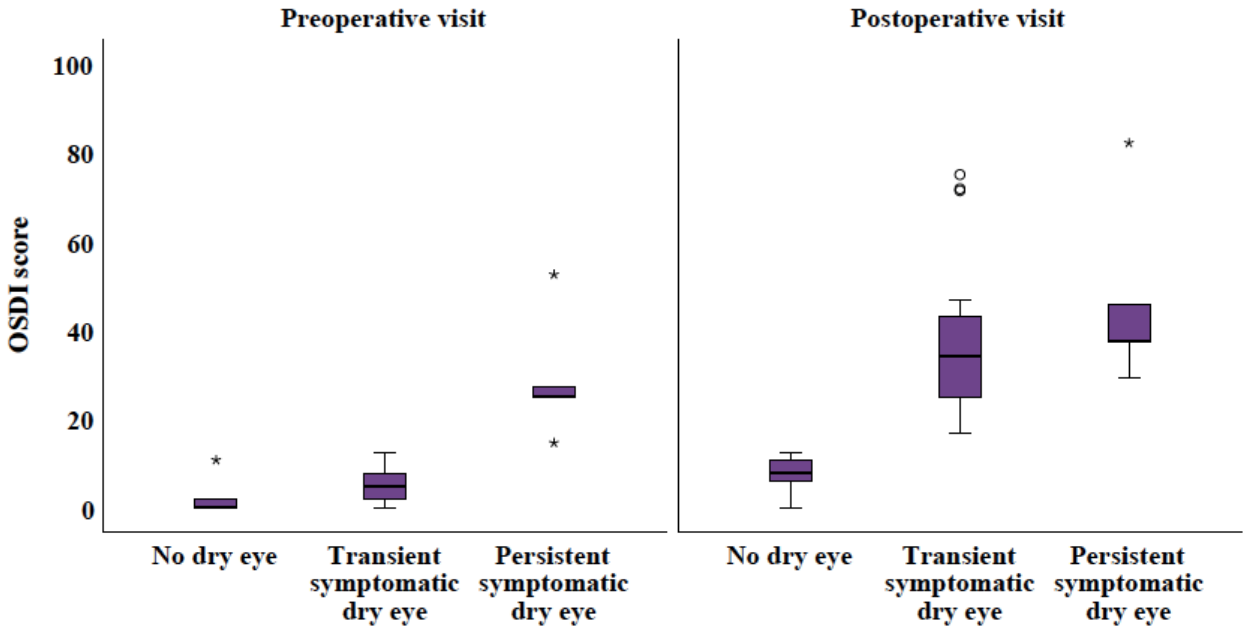
NIBUT at the preoperative visit was significantly different for comparison between the dry eye groups (Kruskal Wallis H=15.33, p=0.006). On post hoc comparisons, NIBUT was significantly lesser in the persistent symptomatic dry eye group when compared to the no dry eye group (Z=-3.20, p=0.004). Other comparisons did not show any statistically significant difference (p>0.05). Similarly, at the postoperative visit, NIBUT was significantly different for comparison between the groups (Kruskal Wallis H=6.39, p=0.03). Although NIBUT was reduced in all the groups, a statistical significant reduction was found in the persistent symptomatic dry eye group when compared to the no dry eye group (Z=-2.60, p=0.02) (**Figure** B).

TMH at the preoperative visit showed a statistical significant difference between the groups (Kruskal Wallis H=6.74, p=0.03). Post hoc comparisons showed a significant lesser TMH in the persistent symptomatic dry eye group when compared to the no dry eye group (Z=-2.57, p=0.03). Postoperatively, TMH was did not show any significant difference between the three groups compared (Kruskal Wallis H=5.53, p=0.06) (**Figure 21**C).

Schirmer's test at the preoperative visit did not show any statistically significant difference between the three groups (Kruskal Wallis H=4.45, p=0.10). At the postoperative visit, Schirmer's test was significantly different between the groups (Kruskal Wallis H=10.06, p=0.007). On post hoc comparisons, significant lesser values were found in the persistent symptomatic dry eye group when compared to the no dry eye (Z=-2.53, p=0.03) and transient symptomatic dry eye group (Z=-3.10, p=0.006) (**Figure 21**D).

Figure 20: Changes in the tear film among the three dry eye groups at the pre and postoperative visit. A) OSDI scores. B) Non-invasive break up time.

A



B

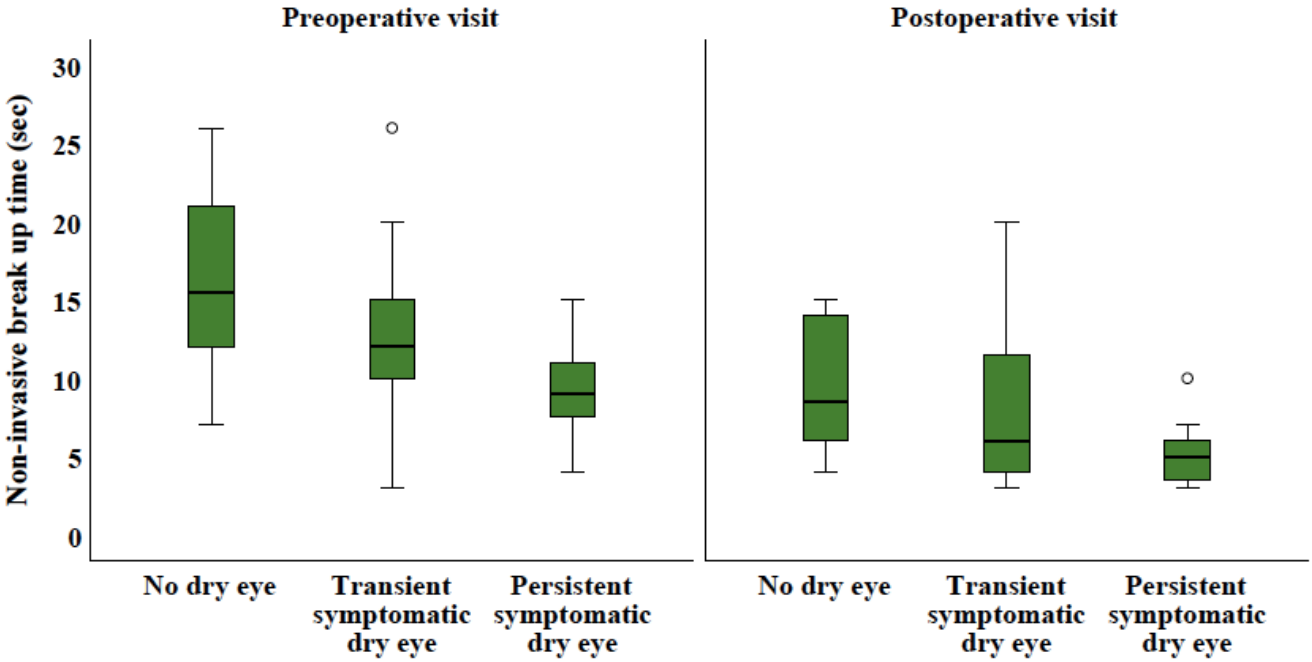
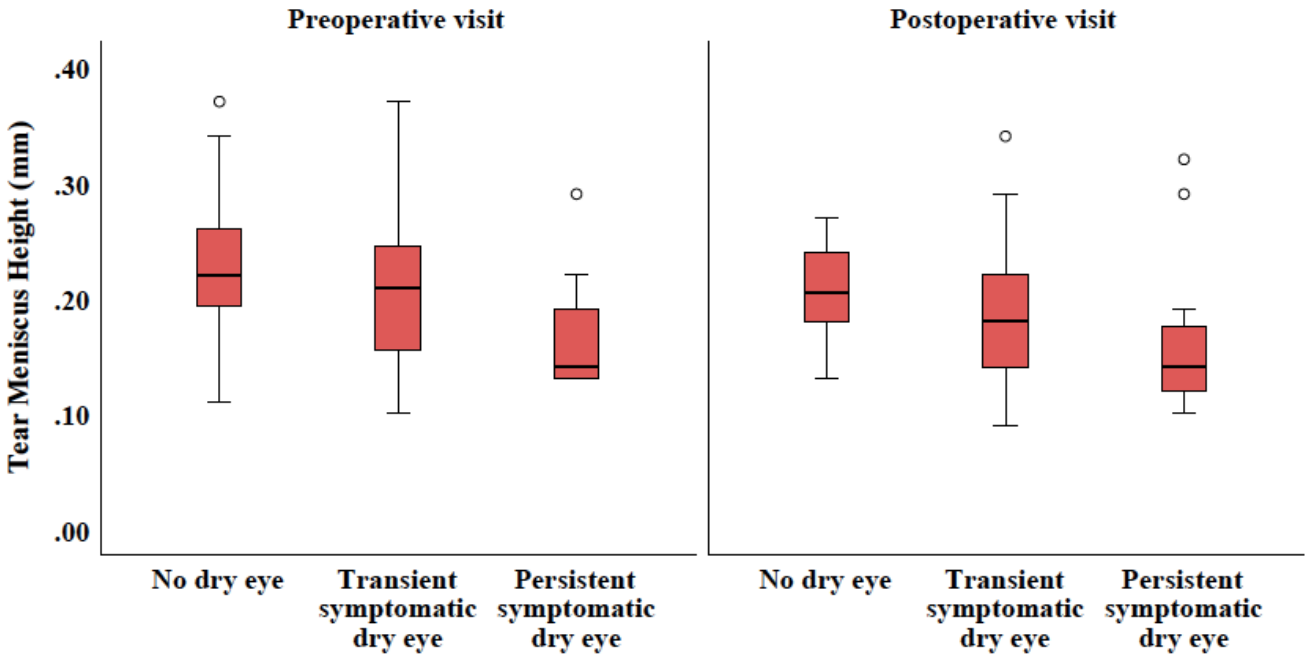
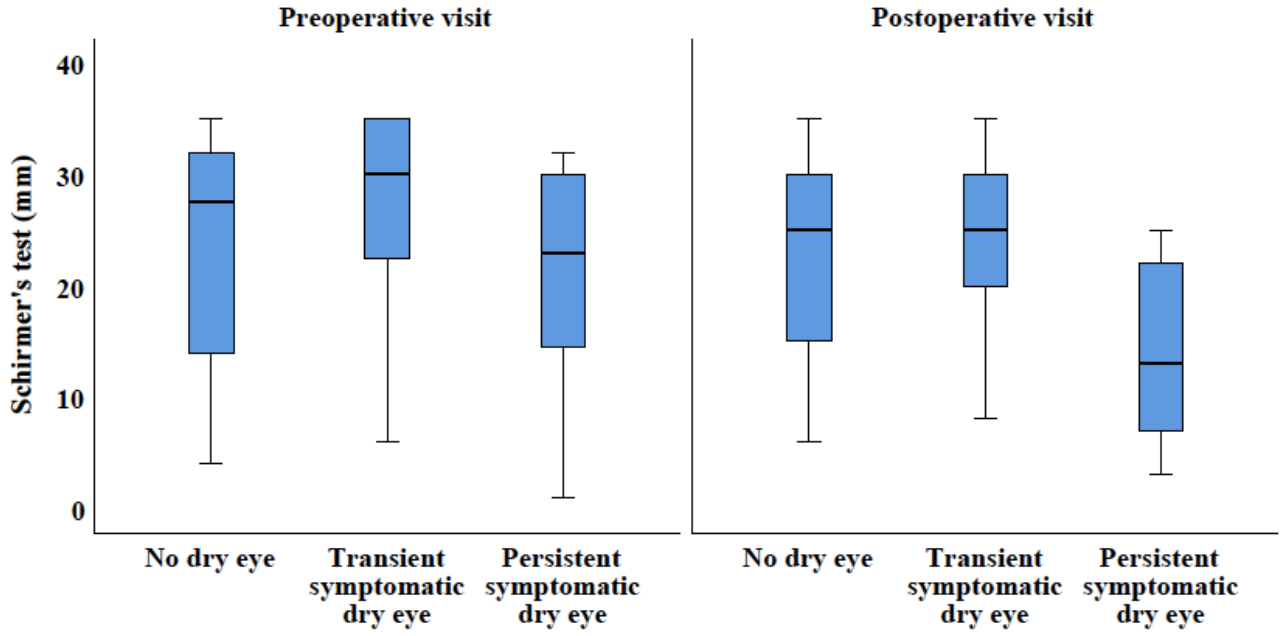


Figure 21: Changes in the tear film among the three dry eye groups at the pre and postoperative visit. (C) Tear meniscus height (D) Schirmer's test

C



D



3.4 Discussion:

This study evaluated the predictive factors and tear film changes of symptomatic dry eyes among subjects presenting for laser refractive surgery. Among the study sample, 17 (23.9%) subjects who opted for laser refractive surgery had symptomatic dry eye based on the OSDI threshold score of 13. It was also found that 67% of the subjects who do not report any symptoms based on their preoperative OSDI scores developed symptoms based on their OSDI scores. Preoperative OSDI scores and tear film tests such as NIBUT and Schirmer's test help in predicting the occurrence of symptomatic dry eyes after laser refractive surgery. Preoperative OSDI scores were statistically significantly higher in the symptomatic dry eye group when compared to the no dry eye group which was not reflected at the postoperative visit. Postoperatively, Schirmer's test values were significantly lower in the symptomatic dry eye group when compared to the no dry eye group.

In this study, the incidence of symptomatic dry eyes was around 23.9% (17 subjects). Similarly, Yu et al[142] reported that fifteen patients (15.6%) had symptoms of dry eyes before LASIK. In the present study, symptomatic dry eyes were assessed using OSDI questionnaires with a threshold value of 13. Whereas, Yu et al[142] did not use any questionnaire to quantify the symptoms. Post-refractive surgery, we found that 82.4% of the subjects had OSDI scores of ≥13. Whereas, Gjerdrum B et al[208] reported that 19.1% of the patients had dry eye disease based on an OSDI score of ≥13. This difference might be due to the time symptoms were assessed, where in this study, the symptoms were assessed in the early postoperative period at 1 week, whereas Gjerdrum B et al[208] reported symptoms among patients who have undergone laser refractive surgery 5-15 years ago. This suggests that among controls,[208,209] and patients presenting for laser refractive surgery dry eye symptoms represented by their OSDI scores exist, which tend to become higher post-surgery and become better with time.

In this study, we have found that preoperative OSDI scores and NIBUT were significant predictors of transient symptomatic dry eyes, whereas preoperative OSDI scores and Schirmer's test were significant predictors of persistent symptomatic dry eyes. Bower et al.[138] reported that preoperative Schirmer's test is a significant predictive factor for the development of chronic dry eye at 12 months. Pre-existing tear film instability is a predictor of dry eye after LASIK and pre-existing signs of dry eye are the predictors for the occurrence of chronic dry eye after LASIK.[210]

Various studies have shown tear film changes after laser refractive surgery,[206,211] where the tear film is affected depending on the type of refractive surgery procedure performed. Tear stability and secretions were reduced at 1month follow-up[142,212] which continued to remain decreased till 6 months after surgery.[145] The results of studies vary depending on the follow-up studied. Similarly, in the present study, it was found that tear stability and secretions are affected in the early postoperative period. Although the results are varying, altogether it can be concluded that the tear film is significantly affected after laser refractive surgery.

Tear film changes between PRK and LASIK showed varying results, where studies have reported that the changes are the same between both procedures.[213] Other studies[145,146] reported that LASIK induces significant changes in tear film when compared to PRK. In the present study, we have seen a significant change in tear stability after PRK when compared to LASIK. This might be due to the irregular corneal surface in the early postoperative period as a result of epithelial healing after PRK.

Among the three dry eye groups, the OSDI score was significantly higher in the persistent symptomatic dry eye group when compared to the no dry eye or transient symptomatic dry eye group. Similarly, Toda I et al[152] reported that dryness scores were higher preoperatively in the probable and definite dry eye groups. However, the probable and

definite dry eye groups are defined based on the presence of symptoms and signs. In this study, we have categorised the subjects based on their OSDI scores. During the postoperative period, transient and persistent symptomatic dry eye groups developed significant higher OSDI scores when compared to no dry eye. As it was reported that 95% of the patients develop at least one dry eye symptom after laser refractive surgery.[142] Therefore, it is preferable to quantify the dry eye symptoms prior to surgery.

NIBUT at the preoperative visit was significantly lower in the persistent dry eye group when compared to the no dry eye group. It was reported that NIBUT was lower in the pre-clinical dry eye group when compared to normals.[209] Postoperatively, the NIBUT was significantly reduced in the persistent symptomatic dry eye group when compared to no dry eye. It was reported that the NIBUT was significantly reduced in subjects with low Schirmer's test[157] and in the definite dry eye group when compared to no dry eye.[152] These points suggest that subjects with persistent symptomatic dry eye have a similar reduction in NIBUT as those subjects with dry eye (diagnosed based on signs and symptoms).

TMH preoperatively showed significantly lower values in the persistent symptomatic dry eye group when compared to no dry eye. In a previous study, TMH was non-significantly lower in the pre-clinical dry eye group compared to normals.[209] Postoperatively, TMH did not change significantly between the three dry eye groups. As there are no similar studies, it is difficult to compare and contrast. In the literature, few studies have reported changes in TMH after refractive surgery,[212,214] while others did not find any change.[147]

Preoperative Schirmer's test did not show any significant difference among the dry eye groups. Postoperatively, there is a significant reduction in the persistent symptomatic dry eye group compared to no dry eye. There are no studies which reported tear film changes based on symptoms alone. But studies[142,152,157] have reported a significant decrease in NIBUT and Schirmer's test values after LASIK and PRK among patients who had preoperative low

Schirmer's values. Albietz et al.[215] compared dry eye symptoms among patients who did or did not receive the ocular surface treatment preoperatively and found that dry eye symptoms were reduced in patients with more vigorous treatment. Hence, preoperative treatment of any existing tear film abnormalities might improve the ocular surface health postoperatively.

3.5 Limitations:

This study assessed the early changes among symptomatic dry eyes after laser refractive surgery. However, studying long-term changes would provide a better understanding of the recovery of tear film tests postoperatively. Future work can be extended by adding meibomian gland morphological and functional changes which could further help in understanding the development of evaporative dry eye or the aqueous deficient dry eye.

3.6 Conclusion:

It can be concluded that the patients presenting for laser refractive surgery might have pre-existing symptomatic dry eyes based on the OSDI scores. Hence, the preoperative symptoms need to be evaluated. Amongst those who do not report symptoms before the procedure, more than half of the patients expressed significant higher OSDI scores at the postoperative visit, however, do not show any significant changes in the tear film after laser refractive surgery. Its occurrence can be predicted by the preoperative tear film stability. Similarly, subjects with pre-existing symptomatic dry eye representation by OSDI score develop more notably higher scores postoperatively. Also, the tear stability and tear secretions were significantly affected postoperatively and its occurrence can be predicted by the preoperative Schirmer's test. Hence, it becomes crucial to evaluate the symptoms as well as the preoperative tear film before surgery to retain patient satisfaction and the overall ocular surface health postoperatively.

Chapter-4: Assessment of Visual Photosensitivity Thresholds after Laser Refractive Surgery using an automated Ocular Photosensitivity Analyser

This chapter has been selected for poster presentation in American Academy of Optometry meet 2022, San Diego. It is also sent for publication to the "Journal of Refractive Surgery"

4.1 Introduction:

Laser refractive surgery is the most commonly performed surgical procedure for correcting the eye's refractive error. Amongst various procedures, the most commonly performed procedures include Photo Refractive Keratectomy (PRK), Laser In situ Keratomileusis (LASIK), and Small Incision Lenticule Extraction (SMILE).[216] Frequently reported side effects post-laser refractive surgery includes dry eye, light sensitivity, and night vision disturbance.[115,217] Previous studies have reported the change in light scattering at the cornea, after refractive surgery.[160,161,163] Where the intraocular light scattering measured using straylight meter was found to be reduced at 15 days post-PRK[161] and LASIK[164] surgery and returned back to normal at 6 months postoperatively. While other studies reported no changes in the forward light scatter and the straylight values 1 month after refractive surgery.[162,163]

Visual light sensitivity or photophobia is defined as intolerance or discomfort with light caused due to intraocular light scattering.[218,219] Symptoms associated with light sensitivity include squeezing or closure of eyes, ocular discomfort and pain.[220] It is one of the most frequent symptoms often seen after refractive surgery, which has been overlooked. This might be due to the lack of reliable, standardized testing protocols and assessment tools for evaluating and quantifying visual light sensitivity. To overcome this, Ocular Photosensitivity Analyser (OPA) was developed for the assessment of visual photosensitivity thresholds (VPTs). This device was found to be repeatable[171] and reliable in measuring VPT among healthy and diseased subjects.[172] The present study aimed to measure the changes in visual photosensitivity thresholds (VPTs) after laser refractive surgery.

4.2 Methods and methodology:

4.2.1 Study Design:

This was a prospective cross-sectional longitudinal study conducted at LV Prasad Eye Institute, Hyderabad, India.

4.2.2 Sample size:

Twenty subjects were recruited for this study. Power calculation was performed at the end of the study with a mean difference of 0.57 log lux unit and a difference in the standard deviation of 0.2, which estimated a power of 90.7% when 20 subjects were included in the study with no lost to follow-up.

4.2.3 Inclusion and exclusion criteria:

Inclusion criteria included subjects suitable for laser refractive surgery after their comprehensive eye examination, with no ocular abnormality except for the refractive error and best-corrected visual acuity of 20/20 or better in both eyes. Subjects with ocular dryness and other systemic conditions that can cause ocular signs such as diabetes mellitus and migraine or any ocular condition leading to photosensitivity were excluded from the study.

4.2.3 Ethics:

The study was approved by the Institutional Ethics Committee of LV Prasad Eye Institute (LEC 09-19-321). All the procedures were performed according to the tenets of the Declaration of Helsinki. Informed consent was signed by all the subjects before participating in the study.

4.2.4 Preliminary examination:

All the subjects had a comprehensive eye examination preoperatively, which includes: ocular and systemic history, uncorrected and corrected distance visual acuity (UDVA, CDVA) manifest retinoscopy, subjective acceptance, slit-lamp biomicroscopic examination, dilated examination of posterior segment, intraocular pressure measurement, computerized assessment of corneal topography and thickness using Oculus Pentacam. Then the subjects were scheduled for laser refractive surgery.

4.2.5 Study procedure:

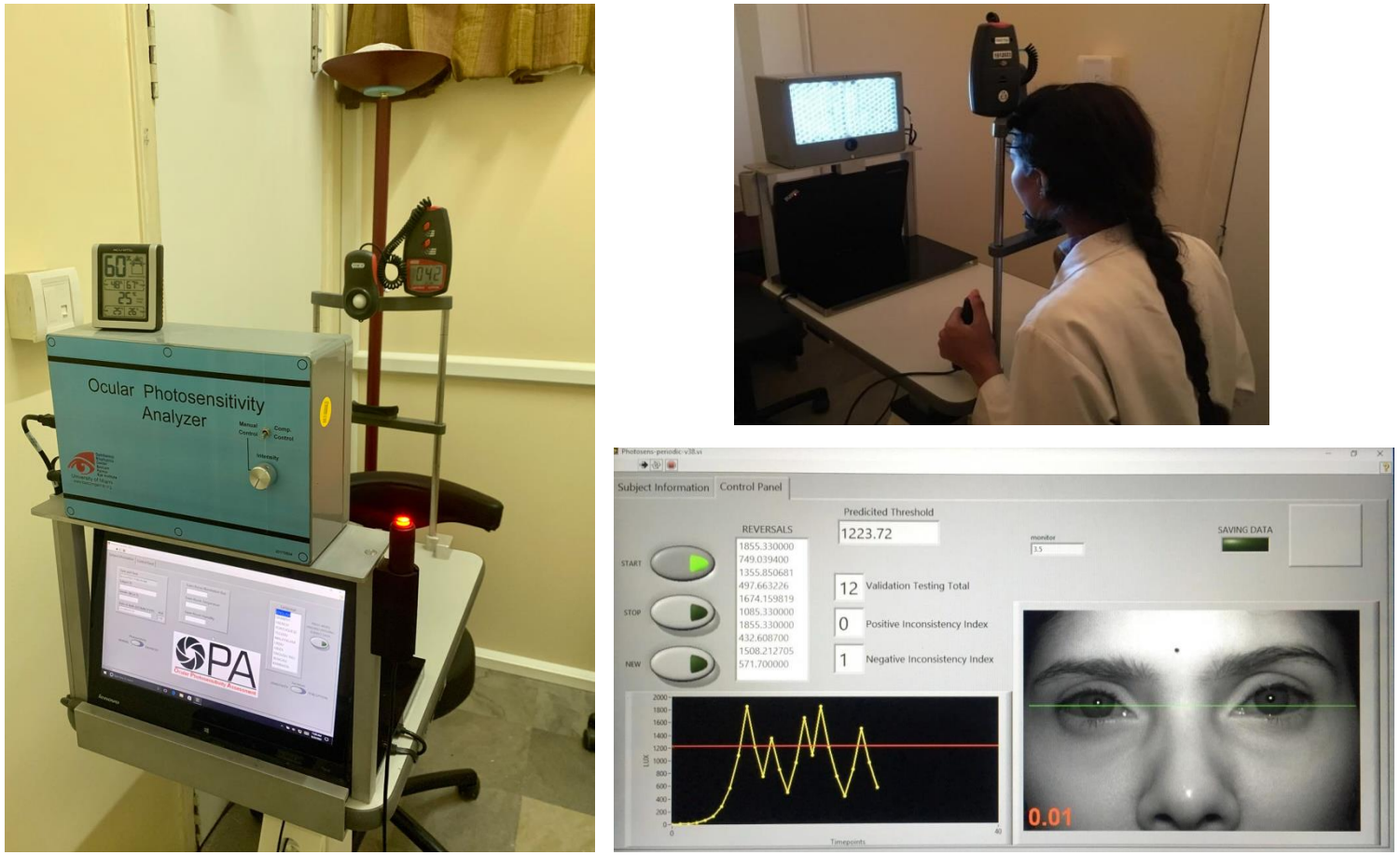
Prior to surgery, all the subjects filled out two questionnaires: Headache Impact Test-6 (HIT-6) and Visual Light Sensitivity Questionnaire 8 (VLSQ-8). The HIT-6 questionnaire assesses the impact of headache on daily activities[221], whereas the VLSQ-8 questionnaire measures the presence and severity of visual light sensitivity (VLS) symptoms.[171] Then, visual photosensitivity thresholds (VPTs) were measured using an ocular photosensitivity analyser (OPA) using the Garcia-Parez staircase technique as described below.[171–173] VLSQ-8 was repeated for all the subjects at the postoperative 1 month visit. Refractive surgery was performed by a single surgeon (PKV) on all the subjects, and the surgery was uneventful.

4.2.5.1 Measurement of visual photosensitivity thresholds:

The Ocular Photosensitivity Analyser is an automated instrument designed for measuring the visual photosensitivity threshold (**Figure *22***). Subjects were asked to rest their chin and forehead on the instrument which is placed at 50 cm. The subject is asked to see the light panel (as shown in) which has a central blinking LED light throughout the experiment. Light stimulus is presented on the light panel with ascending or descending light intensity. Subjects were asked to press the handheld button when the light stimulus felt uncomfortable.

This procedure is repeated until the subject completes 10 response reversals. VPT was measured as the average of ten response reversals. To monitor if the subject is performing correctly, the instrument assesses both false positive and false responses. Binocular measurements were taken first followed by right and left eyes. The VPTs were measured at three visits: preoperatively on the day of surgery, postoperatively at one week, and at one month visit. The order of testing of VPTs was the same for all the subjects at all the visits.

Figure 22: Shows the measurements of visual photosensitivity thresholds using an Ocular photosensitivity analyser.



4.2.6 Statistical analysis:

Statistical analysis was performed using SPSS software Version 25 (SPSS Inc., Chicago, USA). VPT values were converted to logarithmic values (log_{10}lux) due to the logarithmic relationship of photosensitivity with light intensity. Normality was assessed using Kolmogorov-Smirnov test. A mixed-effects model with maximum likelihood estimation was performed to evaluate the change in VPTs at the preoperative visit, 1 week, and 1 month postoperative visits. The type of visit, measurements from binocular and monocular eye/s, and interaction between them (Eye* visit) were included as fixed effects. A random intercept and slope for the visit of the subjects and a random intercept for the eye within a subject was introduced, accounting for inter-eye correlation between the eyes, the longitudinal correlation between the visits, and cross correlation between one eye at one visit and fellow eye at another visit.[222] Statistical significant results were then compared using posthoc tests with Bonferroni correction to adjust for multiple comparisons. For comparison between VLSQ scores preoperatively and 1 month after surgery, paired t-test was performed. For the effect of type of surgery on VPT measurements, a similar mixed-effects model was used with fixed effects for surgery and the visit and with similar random effects as mentioned above. The significance value was set at 0.05.

4.3 Results:

Twenty subjects were included in the study who were followed up till 1 month after refractive surgery. There was no lost to follow-up among the subjects included. The mean age of the subjects included was 25.6 ± 2.94 years, amongst them, 9 (45%) were males, and 11 (55%) were females. Preoperatively, the mean spherical equivalent error in the right eye was -4.74 ± 2.41 D and left eye was -4.53 ± 2.33 D. Mean preoperative HIT-6 and VLSQ-8 scores were 43.15 ± 4.67 and 14.9 ± 3.72 respectively. None of the subjects had HIT-6 score >50 or VLSQ-8 score >22 in the preoperative visit. **Figure *23*** shows the binocular and monocular VPTs for the three visits.

4.3.1 Comparison of VPT at pre and postoperative visits:

VPTs (in log lux units) showed a statistical significant difference between the three visits (F=13.80, *P*=0.0001). Amongst the three visits, VPTs were found to be significantly reduced at postoperative 1 week when compared to preoperative visit (**Table *10***). There was no statistically significant difference in the VPTs at postoperative 1 month when compared to preoperative visit (*P*=0.08). Post hoc comparison showed a statistically significant decrease in VPT at postoperative 1 week visit (*P*=0.001) which significantly improved at postoperative 1 month visit (*P*=0.0001). There was no statistically significant difference between VPT at preoperative and postoperative 1 month visit (*P*=0.82).

Figure 23: Mean binocular, right and left eye visual photosensitivity thresholds (VPTs) measured before and after laser refractive surgery at the following visits. Error bars indicate the standard error of the mean.

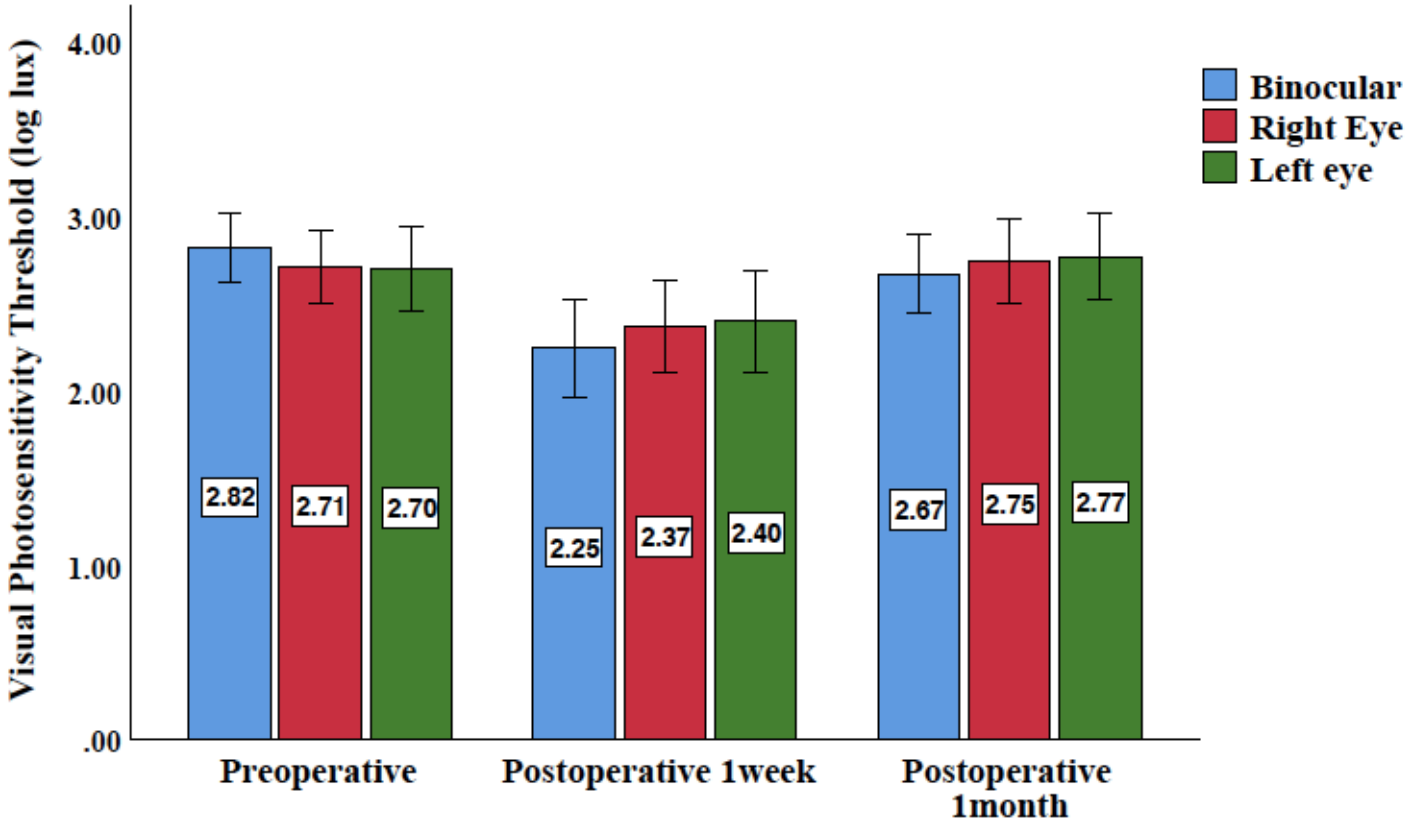


Table 10: Changes in Visual Photosensitivity thresholds (VPT) after laser refractive surgery

Fixed effects				**Random effects**	
Variable	**Coefficient ± SE**	**95% CI**	***P* value**	**Level**	**SD**
Intercept	2.819 ± 0.100	2.612 to 3.026	**0.0001**	Residual	0.158
PO 1week - preoperative	-0.574 ± 0.113	-0.807 to -0.340	**0.0001**	Subject	0.339
PO 1month - preoperative	-0.146 ± 0.084	-0.316 to 0.022	0.087	Visit	0.772
				Eye within subject	0.089

PO- postoperative; SE- Standard error; SD- standard deviation

4.3.2 Comparison of binocular, right and left eye VPTs at the three visits:

Binocular and monocular VPTs did not show any statistical significance (F=0.67, *P*=0.51). However, the interaction of binocular and monocular VPTs with the type of visit showed a statistically significant difference (F=4.76, *P*=0.002). With posthoc comparisons, the VPTs of right and left eye did not differ significantly from binocular VPT at the preoperative visit (*P*<0.05) (**Table *11***). At the postoperative 1 week visit, the binocular VPT decreased when compared to the right, and left eye VPTs, however statistically significant difference was found only for comparison left eye VPT (*P*=0.02). There was no statistically significant difference in the VPTs of right, left, or binocular at postoperative 1 month visit (*P*>0.05).

4.3.3 Assessing change in VPT at pre and postoperative visits after adjusting for preoperative characteristics:

A similar pattern was observed for change in VPTs among the visits after adjusting for the effects of age, spherical equivalent error, preoperative HIT-6, and VLSQ-8 scores (**Table *12***).

4.3.4 Changes in VLSQ-8 scores between preoperative and postoperative 1 month visit:

The preoperative VLSQ-8 score was 14.9 ± 3.72, while the postoperative score was 17.7 ± 4.65. Postoperative VLSQ-8 scores were higher than the preoperative scores and this was statistically significant (t=-5.91, *P*=0.0001).

Table 11: Comparison of binocular and monocular Visual Photosensitivity thresholds (VPT) after laser refractive surgery:

Visit	Comparison	Mean difference ± SE	*P* value	95% CI
Preoperative	Right eye – Left eye	0.010 ± 0.058	0.999	-0.150 to 0.130
	Left eye - Binocular	-0.116 ± 0.058	0.141	-0.256 to 0.024
	Binocular – Right eye	0.106± 0.058	0.209	-0.034 to 0.246
PO 1week	Right eye – Left eye	-0.030 ± 0.058	0.999	-0.170 to 0.110
	Left eye - Binocular	0.157 ± 0.058	**0.022**	0.017 to 0.297
	Binocular – Right eye	-0.127 ± 0.058	0.087	-0.267 to 0.013
PO 1month	Right eye – Left eye	-0.021 ± 0.058	0.999	-0.161 to 0.119
	Left eye - Binocular	0.096 ± 0.058	0.293	-0.044 to 0.236
	Binocular – Right eye	-0.075 ± 0.058	0.582	-0.215 to 0.065

PO- postoperative; SE- Standard error; CI- confidence interval

Table 12: Changes in Visual Photosensitivity thresholds (VPT) after laser refractive surgery adjusted by the effects of age, gender, spherical equivalent error, preoperative HIT-6, and VLSQ-8 scores

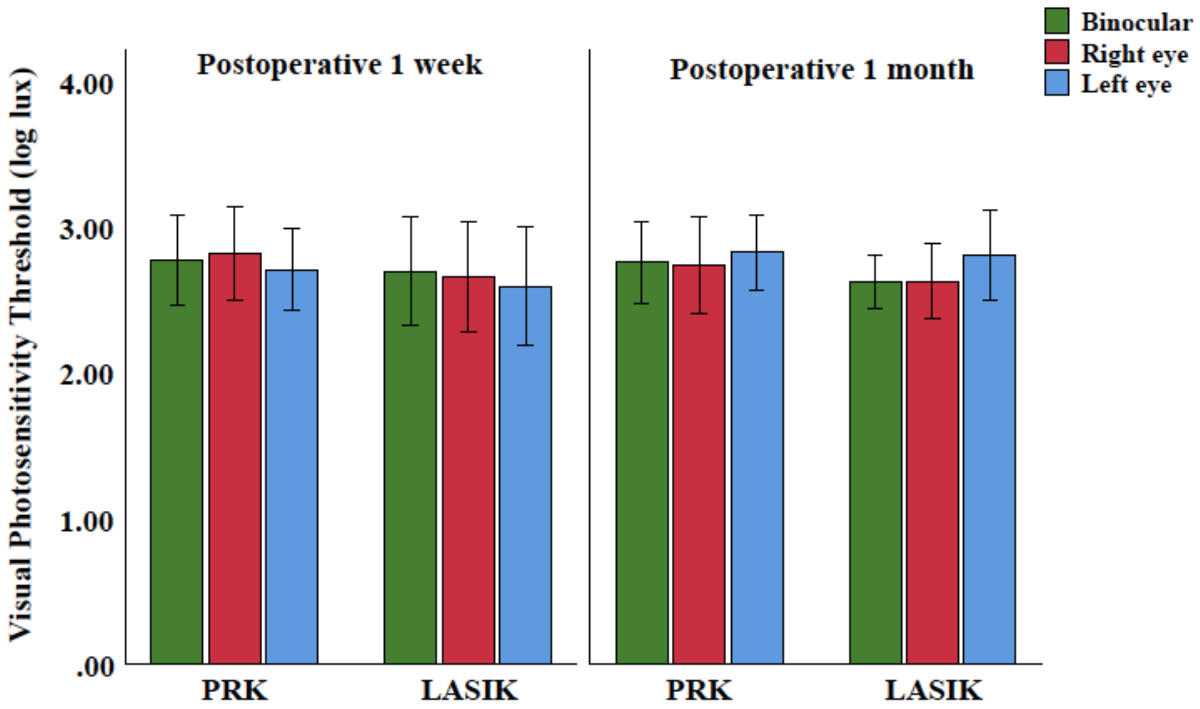
Fixed effects				**Random effects**		
Variable	**Coefficient ± SE**	**95% CI**	***P* value**	**Level**		**SD**
Intercept	4.286 ± 1.160	1.865 to 6.707	**0.001**	Residual		0.158
PO 1week - preoperative	-0.574 ± 0.113	-0.807 to -0.340	**0.0001**	Subject		0.326
PO 1month - preoperative	-0.146 ± 0.084	-0.316 to 0.022	0.087	Visit		0.750
Age	-0.034 ± 0.032	-0.102 to 0.033	0.298	Eye within subject		0.089
Gender (ref=female)	-0.063 ± 0.194	-0.469 to 0.343	0.750			
Spherical equivalent error	-0.063 ± 0.127	-0.328 to 0.201	0.625			
Preoperative HIT-6	-0.003 ± 0.021	-0.047 to 0.040	0.874			
Preoperative VLSQ-8	-0.045 ± 0.032	-0.114 to 0.0226	0.178			

PO- postoperative; SE- Standard error; SD- standard deviation

4.3.5 Effect of type of surgery on VPT measurements after laser refractive surgery:

Among all the subjects, 13 (65%) of them underwent PRK, and 7 (35%) of them underwent LASIK. There was no statistical significant difference for the VPT among the two surgical procedures compared (F=0.204, *P*=0.657) (**Figure *24***) indicating that there is no effect of the type of surgery on VPT.

Figure 24: Binocular, right and left eye VPT after laser refractive surgery among PRK and LASIK



4.4 Discussion:

This study assessed the visual light sensitivity or photophobia quantitatively by measuring the visual photosensitivity thresholds (VPT) using an Ocular Photosensitivity Analyser (OPA) after laser refractive surgery. Where it was found that the VPTs significantly decreased at postoperative 1 week visit then significantly improved by postoperative 1 month visit. There was no statistically significant difference found in the VPTs preoperatively and at the postoperative 1 month. Binocular and monocular VPTs did not differ at the preoperative visit. However, binocular VPT was significantly reduced at postoperative 1 week visit when compared to the monocular VPTs. VLSQ-8 scores were significantly higher at postoperative 1 month visits when compared preoperatively. This study did not find any significant change in VPTs after PRK or LASIK surgery.

Aguilar MC et al.[172] have reported lower VPT among light-sensitive subjects such as achromatopsia and traumatic brain injury compared to healthy subjects. In this study, it was found that the binocular and monocular VPTs reduced after laser refractive surgery at the early postoperative visit. Subjects undergoing refractive surgery report visual disturbances immediately after the procedure, which improves between 6months and 1 year post refractive surgery.[223] Similarly, in this study, it was found that the VPT returned back to preoperative values at postoperative 1 month visit. Other studies reported an increase in glare,[159,224] night vision disturbance,[223,225,226] decreased contrast sensitivity[227–229] and increased intraocular light scatter,[161,164] within 6 months post refractive surgery, which goes hand in hand with the symptoms of photophobia.

Preoperatively, binocular VPT was similar to the VPTs of the right and the left eye (**Figure *23***). However, at the postoperative 1 week visit, the binocular VPT was significantly reduced than monocular (right and left eye) VPTs. Jimenez JR et al.[230] reported that binocular function deteriorates more than the monocular function after LASIK. Similarly, an increase

in the forward light scatter results in interocular differences, which lead to the reduced binocular performance.[231] This reduces the binocular summation postoperatively after laser refractive surgery.

In the present study, no significant effects of age, gender, HIT-6, and VLSQ-8 scores were found on binocular and monocular VPTs. A previous study reported a significant positive effect of VPT with age and a negative effect on VLSQ-8 scores.[173] This might be due to the smaller range of the age group of the subjects included. VLSQ-8 scores were significantly higher after laser refractive surgery, indicating that the subjects experience symptoms of light sensitivity after laser refractive surgery. Subjects with achromatopsia[232] and macular pigment optical density[233] also show higher VLSQ scores when compared to healthy subjects.

4.5 Limitations:

This study quantified the photophobia among pre and post-refractive surgery subjects by measuring the visual photosensitivity thresholds (VPT). This work can also be extended by assessing the change in binocular and monocular VPTs at longer follow-up visits among these subjects. Future work can be recommended for more studies on comparing VPT among various refractive surgery procedures, including SMILE, with a larger sample in each group.

4.6 Conclusion:

In summary, this study assessed the change in binocular and monocular visual photosensitivity thresholds (VPT) after refractive surgery, where a significant reduction in VPT was found at postoperative 1 week visit, which returned back to normal values at 1 month postoperative visit. Binocular VPT was reduced after laser refractive surgery when compared to monocular VPTs.

Chapter-5: Summary, Conclusions and Future Directions

5.1 Significance of research:

Dry eye is the most common ocular condition which is known to affect the quality of a person's life. Identifying this condition at an early stage can prevent further changes that may occur in the tear film. Changes in the tear film among subjects diagnosed with dry eyes (based on symptoms and signs) are well known as per the DEWS-II report. Few studies have examined these changes in subjects who report only symptoms with no signs. Furthermore, any intervention such as laser refractive surgery that occurs in the presence of ocular dryness leads to severe dry eye after the procedure. It was also reported that among patients with pre-existing dry eyes (with the presence of signs), the tear stability and secretions worsened after laser refractive surgery. However, among subjects who report only symptoms, the changes in the tear film remain unexplored. In addition to dry eye, patients also experience glare, photophobia, and night vision disturbances, amongst which all of them have been studied except photophobia.

5.2 Summary of the findings and Implications of Research Work

Tear film changes and MG morphology of both the upper and the lower lids were assessed in the pre-clinical dry eye and compared with normals grouped based on their OSDI scores in a prospective cross-sectional study (Chapter 2). Where it was found that nearly half of the study sample had a pre-clinical dry eye defined by their OSDI scores. In these subjects, NIBUT alone was lesser to differentiate from normals. TMH, Schirmer's test, and corneal staining play no significant role in detecting pre-clinical dry eye. Similarly, a decrease in the MG length of the lower lid indicates an early sign of dry eye changes among pre-clinical dry eyes. Other MG morphological changes such as MG width, MG loss and tortuosity did not vary between the pre-clinical dry eye and normals. It was also found that almost half of the

study (49.6%) sample were found to have computer vision syndrome based on the CVS-Q scores. These subjects had high OSDI scores, lower TMH and MG length in the lower lid. Hence, it is important to assess the symptoms of dry eye by administering the OSDI questionnaire and further perform non-invasive tests such as NIBUT and IR imaging of MG in a routine clinical examination to detect pre-clinical dry eye.

By looking at the findings from the above objective, we wanted to evaluate the changes in the tear film among symptomatic dry eyes after laser refractive surgery, where a prospective case-control study was conducted (Chapter 3). It was found that one-third of the patients presenting for laser refractive surgery have pre-existing symptomatic dry eyes based on the OSDI scores. These subjects develop more notably higher scores postoperatively. Also, the tear stability and tear secretions were significantly affected postoperatively and its occurrence can be predicted by the preoperative Schirmer's test. Amongst those who do not report symptoms before the procedure, more than half of the patients express significant higher OSDI scores at the postoperative visit, however, do not show any significant changes in the tear film after laser refractive surgery. Its occurrence can be predicted by the preoperative tear film stability. Therefore, it is crucial to evaluate the symptoms as well as the preoperative tear film to prevent severe or chronic dry eye and achieve success as well as patient satisfaction.

Besides the dry eye, other side effects are also seen after laser refractive surgery. Amongst which changes in photophobia or visual light sensitivity after laser refractive surgery has been evaluated (Chapter 4). It was found that the visual photosensitivity thresholds were significantly reduced at the postoperative 1-week visit, which returned back to near normal values by 1 month postoperative visit. Binocular VPT was significantly reduced when compared to monocular VPTs during the postoperative 1-week visit. It can be

concluded that the visual light sensitivity becomes higher in the early postoperative period, which significantly affects binocular performance.

5.3 Limitations and Future Directions:

While the current study found changes in the tear film and MG morphology among pre-clinical dry eyes. This study did not assess the functional changes such as meibum quality, gland expression, lid margin irregularity, and telangiectasia. As, vital signs for MGD are morphological changes,[101] which occur before the onset of symptoms.[121] Studying these changes with MG morphology would provide a better understanding of different grades of MGD and its association with dry eye. In future studies, it is recommended to assess the tear film between VDT and non-VDT users using the standard questionnaire.

Post-laser refractive surgery, significant changes in tear film have been found among symptomatic dry eyes. However, this study assessed the early changes among symptomatic dry eyes after laser refractive surgery. This is considering the symptoms documented based on the OSDI questionnaire, which documents the symptoms in a week's time.[207] Also, not to get biased by the change in the symptoms (some may worsen or improve in the last week) at the next follow-up visit. However, studying long-term changes would provide a better understanding of the recovery of tear film tests postoperatively. Future work can be extended by adding meibomian gland morphological and functional changes which could further help in understanding the occurrence of the evaporative dry eye or the aqueous deficient dry eye.

The study from chapter 4 quantified the photophobia among pre and post-refractive surgery subjects by measuring the visual photosensitivity thresholds (VPT), where the VPT was found to be reduced after laser refractive surgery at the early postoperative visit. This work can also be extended by assessing the change in VPTs among various refractive surgery procedures, including SMILE. Future work can be also recommended on looking at the

changes in VPT among patients with corneal haze and regression after laser refractive surgery.

5.5 Conclusion:

The conclusion from the research in this thesis found that most young individuals presenting for the regular eye examination have pre-clinical dry eye based on their OSDI scores, where tear film and MG morphology changes are seen compared to normals. Hence, it is important to administer the OSDI questionnaire as a part of the routine eye examination to check if they fall under pre-clinical dry eye, then perform non-invasive tests such as NIBUT and IR imaging of MG as a part of further screening. Similarly, laser refractive surgery is performed among adults in the age range of 19 and 40 years. The current study reported that 24% of the subjects had pre-existing symptomatic dry eyes. Hence, for subjects who present for laser refractive surgery, preoperative assessment of tear film and OSDI scores is crucial and needs to be included as a part of a comprehensive eye examination. Furthermore, most (67%) of the subjects who do not have dry eye symptoms preoperatively based on OSDI scores develop transient symptomatic dry eyes represented by an increase in the OSDI scores. Significant postoperative tear film changes are seen among these subjects, and their occurrence can be predicted by preoperative OSDI scores and non-invasive breakup time. Similarly, in subjects with pre-existing symptomatic dry eye representation by OSDI score, the tear stability, and tear secretions are significantly affected postoperatively, and its occurrence can be predicted by the preoperative OSDI scores and the Schirmer's test. Also, there is a decrease in visual photosensitivity thresholds, indicated by an increase in visual light sensitivity after laser refractive surgery during the early postoperative period, which recovers to near normal by 1month postoperative visit.

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APPENDICES

APPENDIX- A PUBLICATIONS

Experimental Eye Research 222 (2022) 109188

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Research article

Changes in the tear film and meibomian gland morphology between preclinical dry eye and normal subjects represented by ocular surface disease index scores

Asra Fatima [1], Pavani Vadla [1], Nagaraju Konda [*]

School of Medical Science, University of Hyderabad, Hyderabad, India

ARTICLE INFO

Keywords:
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Tear film
Dry eye
Ocular surface disease index score
Computer vision syndrome-Questionnaire
ImageJ software
Meibomian gland tortuosity
Meibography

ABSTRACT

Tear film and MG morphology play an essential role in detecting dry eyes and Meibomian Gland Dysfunction (MGD). Previous studies have reported these changes in cases diagnosed with dry eyes. However, it is important to study these changes among subjects with symptoms of dry eyes without signs. Hence, this study evaluated the changes in the tear film and meibomian gland (MG) morphology among subjects with pre-clinical dry eye and compared it with the normals defined by the Ocular Surface Disease Index score. One hundred and fifty subjects were enrolled in this prospective cross-sectional study. All the subjects completed the Ocular Surface Disease Index (OSDI) questionnaire and the Computer Vision Syndrome Questionnaire (CVS-Q). Tear film tests such as non-invasive break-up time (NIBUT), tear meniscus height (TMH), lipid layer pattern, Schirmer's test, and corneal staining were performed. Images were captured from both the upper and the lower eyelids to study the MG morphology. TMH, MG length, thickness, loss, and tortuosity were measured using ImageJ software. Subjects were differentiated into two groups based on an OSDI threshold score of ≥ 13 as preclinical dry eye and normals. Among all the subjects, 43.6% of them were categorized as pre-clinical dry eye, and 56.4% as normals. In the pre-clinical dry eye group, a significant reduction in NIBUT ($Z = -2.13$, $p = 0.03$) and MG length of the lower lid ($Z = -2.58$, $p = 0.01$) was found when compared to normals. TMH, Schirmer's test, and MG width did not vary among both groups ($p > 0.05$). Similarly, MG loss and tortuosity score was higher in the pre-clinical dry eye group, but did not show any statistical significance ($p > 0.05$). The majority of the young individuals presenting for the regular eye examination may have pre-clinical dry eye based on their OSDI scores. Hence, it is important to administer the OSDI questionnaire and perform non-invasive tests such as NIBUT and IR imaging of MG as a part of the routine eye examination.

APPENDIX-B CONFERENCE PRESENTATIONS

ARVO International Chapter Affiliate

ARVO-INDIA

Indian Eye Research Group

October 7-10, 2021

Certificate of Participation

This is to certify that

ASRA FATIMA

participated in the virtual meeting and contributed to the proceedings.

Dr Ronnie George
President, ARVO-India

Dr Sayan Basu
On behalf of Organisers

IOA 2020

EVIDENCE BASED PRACTICE
TRANSFORMING PRIMARY EYE CARE
04-06 DECEMBER
INDIAN OPTOMETRIC ASSOCIATION (IOA)-2020
VIRTUAL CONFERENCE

Organised By

Date: 06th November. 2020

To
Ms. Asra Fatima, B.Optom, M.Phil
Ph.D. Scholar, University of Hyderabad

Subject: Letter of invitation to deliver a talk at the Indian Optometric Association 2020 virtual conference – "Evidence based Practice – Transforming Primary Eye Care" scheduled on **4, 5 & 6 December 2020**

Dear Ms. Fatima

It gives us great pleasure in inviting you **to deliver a talk** during the forthcoming "**Indian Optometric Association (IOA) - 2020**" scheduled on **4, 5 & 6 December 2020** through a virtual platform being organized by Indian Optometric Association, India.

The conference's theme is "**Evidence-based Practice – Transforming Primary Eye Care**".
We invite you to deliver a talk in the "**Anterior segment and Beyond borders**" session. We would be greatly honored if you accept our request for this virtual meeting. The details of your talk are

Title: **Refractive Surgery Complications;** Date: **06th December 2020; Sunday;** Duration: 15 mins; Time: 13.15 – 13.30 (IST)

It is our pleasure to inform you that your registration will be complimentary. Your gracious presence at the meeting will be a source of invaluable encouragement and inspiration for the conference. We sincerely hope you will accept our invitation and confirm.

Thanking you in anticipation.

Dr Rajeev Prasad
Organizing Secretary
IOA 2020

Dr Nagaraju Konda
Chairman – Scientific Committee
IOA 2020

Dr Ganesh Babu Jonnadula
Session In-charge
IOA 2020

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August 3, 2022

Asra Fatima
SRT-332, Sanath Nagar
Hyderabad, Telangana, 500018
India

Dear Dr. Asra Fatima:

You are cordially invited to join us at Academy 2022 San Diego! This meeting will be held in San Diego, California, from **Wednesday, October 26—Saturday, October 29, 2022**. We would like to confirm that your abstract "Assessment of Visual Photosensitivity Thresholds after Laser Refractive Surgery using an Automated Ocular Photosensitivyty Analyser" was accepted to be presented as a scientific poster and we hope that you can join us in person at Academy 2022 San Diego this year.

The Academy's Continuing Education Program consists of Lectures, Workshops, Papers, Posters and Symposia. The Scientific Program offers leading scientists, educators, and clinicians the opportunity to exchange the latest information in optometry and vision science. We look forward to seeing you in San Diego for the absolute best in optometric education!

Please be advised effective January 12, 2009, the United States Government has changed certain requirements for visas and other rules regarding entering the country. In addition, the U.S. Department of Homeland Security has announced that it will require visitors who are allowed to enter the country without visas to register biographical data online at least three days prior to travel.

Sincerely,

Richard Jones, CPA
Interim Chief Executive Officer

Affiliate Organization
American Academy of Optometry Foundation

APPENDIX-C ACHIEVEMENTS

APPENDIX-D INFORMED CONSENT FORM

RESEARCH PARTICIPANT INFORMED CONSENT FORM (Objective-1)

Protocol Title: Normative Data on Dry eyes among Indian Population (UH/IEC/2019/148)

Investigators: Asra Fatima, Pavani, Nagaraju Konda

What you should know about this study:

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Ask questions about anything you do not understand now, or when you think of them later.
- You are a volunteer. If you do join the study and change your mind later, you may quit at any time

Why is this research being done?

This research is being done to know the normal values for dry eye tests among Indian population. This will be performed using a device, easy tear view and few measurements on slit lamp. We expect around 150 healthy normal subjects for the study.

What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

a) Questionnaire: Ocular surface Disease Index Questionnaire (OSDI) and Computer Vision Syndrome Questionnaires

b) Schirmer's test: This test measures the tear production in your eyes. This procedure is commonly performed in clinical setup.

c) Tear break-up time (TBUT): This test is used to measure how stable are the tears in the eye. This procedure is also commonly performed in the clinical setup.

d) Corneal fluorescein staining: This procedure is commonly performed in the clinical setup, where fluorescein dye is instilled into the eye and corneal surface is observed.

i) Tear film imaging using Easy tear view plus: Few tear film tests such as lipid layer thickness, meibomian gland imaging, tear meniscus, will be imaged using the device.

What are the risks or discomforts of the study?

There are no risks involved in the study. The tests undertaken in this study are routinely performed in the general eye examination.

Are there benefits to being in the study?
There is no direct benefit to you from being in this study. If you take part in this study, you may help others in the future.

What are your options if you do not want to be in the study?
Participation in the study is purely voluntary.

Will it cost you anything to be in this study?
The study procedures will be provided at no cost to you.

Will you be paid if you join this study? No

What information about you will be kept private and what information may be given out?

The University of Hyderabad has a policy to protect health information that may identify you. This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as described in this form.

What should you do if you are injured or ill as a result of being in this study?

If you think you are injured or ill as a result of being in this study, call the principal investigator, Asra Fatima, at 7207299796

What does your signature on this consent form mean?

By signing this consent form, you are not giving up any legal rights. Your signature means that you understand the information given to you in this form, you accept the provisions in the form, and you agree to join the study.

Name of the person taking consent:

_____

Signature of the person taking consent: Date:

_____

Name of the subject/ participant:

_____

Signature of the participant:

_____ Date:

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM
(Objective-2)

Protocol Title: Dry eyes after refractive surgery among Indian Population (LEC 03-19-232)

Application No.:01

Principal Investigator: Asra Fatima, Ph.D Scholar, University of Hyderabad

Date: 25/Feb/ 2019, Version: 01

1. What you should know about this study:

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Ask questions about anything you do not understand now, or when you think of them later.
- You are a volunteer. If you do join the study and change your mind later, you may quit at any time without fear of penalty or loss of benefits.
- While you are in this study, the study team will keep you informed of any new information that could affect whether you want to stay in the study.
- If children may join this study, the word "you" in this consent form will refer to both you and your child.

2. Why is this research being done?

This research is being done to know the incidence (number of people with dryness at given time period) of dryness among refractive surgery subjects. Also to understand the changes in the light sensitivity experienced after refractive surgery
People who are willing to undergo refractive surgery may join the study.

We expect around 70 subjects/ patients for the study

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

a) Ocular surface Disease Index Questionnaire (OSDI): This is a questionnaire that should be graded based on your symptoms.
b) Schirmer's test: This test measures the tear production in your eyes. This procedure is commonly performed in clinical setup.

c) Non-Invasive Tear break-up time (NIBUT): This test is used to measure how stable are the tears in the eye. This procedure is also commonly performed in the clinical setup.

d) **Tear meniscus assessment:**
The meniscus, or tear lake is the amount of tears resting at the junction of the bulbar conjunctiva and the lower eyelid margin. This is measured using a scale or graticule on slit lamp examination.

4. What are the risks or discomforts of the study?

There are no risks involved in the study. The tests undertaking in this study are routinely performed in the general eye examination, may cause minimal glare and discomfort while performing some of the routine investigative techniques.

5. Are there risks related to pregnancy?

Nil

6. Are there benefits to being in the study?

There is no direct benefit to you from being in this study. If you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

Participation in the study is purely voluntary. If you do not join, your care at L.V. Prasad Eye Institute will not be affected.

8. Will it cost you anything to be in this study?

The study procedures will be provided at no cost to you.

9. Will you be paid if you join this study?

No

10. Can you leave the study early?

1. *If you wish to stop, please tell us right away.*
2. *Leaving this study early will not stop you from getting regular medical care.*
3. *If you leave the study early, L.V. Prasad Eye Institute may use or give out your health information that it already has if the information is needed for this study or any follow-up activities.*

11. What information about you will be kept private and what information may be given out?

L.V. Prasad Eye Institute has a policy to protect health information that may identify you. This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as described in this form.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out as described in this form. Information that identifies you can include your name, address, telephone number, date of birth, and other details about you. Information that relates to your health or medical condition includes:

- Information we get from you or from the activities and procedures described in this consent form, which may include:

  i) things done to see if you can join this study, such as physical eye checkup, few tests to measure the dryness in the eyes, tear collection and any other information that you share with us, including information about your health history and your family health history; and

  ii) information obtained during the study, such as conducting the similar tests at your follow-up visits as advised by the consultant, and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?
Some people may see your health information and may give out your health information as needed to conduct this study. These people include the researcher and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?
Other organizations involved with protecting research participants, or just with this study, may see your health information. These include:

- An institutional review board from UOH.
- Investigators from UOH participating in the study.

d. Why will this information be used and given out?
Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?

You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. How long does this privacy authorization last?

This authorization to use and give out health information does not end unless you cancel it. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after the date that you leave. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?

Even though L.V. Prasad Eye Institute has agreements with other organizations to protect the use of health information, if your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and might be used or given out without your permission.

12. What does a conflict of interest mean to you as a participant in this study?

Conflict of interest is a situation where a person or an organization has a financial or other interest large enough to appear as if it could influence their judgment. The investigator in this study has a conflict of interest in connection with this study and the following paragraph(s) tell(s) you about it.

13. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The L.V. Prasad Eye Institute IRB is made up of scientists ,non-scientists, doctors, and legal personnel. The IRB's purpose is to review human research studies and to protect the rights and welfare of the people participating in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is

b. What do you do if you have questions about the study?

Call the principal investigator, Asra Fatima, at 7207299796

c. What should you do if you are injured or ill as a result of being in this study?

If you have an urgent medical problem related to your participation in this study, call *Dr. Pravin Krishna* at *040-30612100.*

If you think you are injured or ill as a result of being in this study, call the principal investigator, Asra Fatima, at 7207299796

The medical services at L.V. Prasad Eye Institute will be open to you as they are to all sick or injured individuals. L.V. Prasad Eye Institute does not have a program to pay you if you are hurt or have other bad results from being in the study. You are financially responsible for payment of any treatment or hospitalization. At your request, your insurance provider will be billed for payment of any treatment or hospitalization.

d. What happens to Data, Tissue, Blood and Samples that are collected in the study?

L.V. Prasad Eye Institute is dedicated to finding the causes and cures of ocular disease. The tear samples collected from your eyes are important to this study and to future research. If you join this study, L.V. Prasad Eye Institute or its outside partners in this research will own this data and tear samples. This tear sample will be studied, tested and analyzed by medical scientists. You will not receive any financial benefit from this.

e. What are the Organizations that are part of L.V. Prasad Eye Institute?

University of Hyderabad does few collaborative research works with LV Prasad Eye Institute.

14. What does your signature on this consent form mean?

By signing this consent form, you are not giving up any legal rights. Your signature means that you understand the information given to you in this form, you accept the provisions in the form, and you agree to join the study.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

NOT VALID WITHOUT THE IRB STAMP OF CERTIFICATION

Do not sign after the expiration date of: _____

FOR ADULTS AND CHILDREN CAPABLE OF GIVING CONSENT**:**

_____

Participant's Signature

Date

SIGNATURE(S):

_____

Signature of Person Obtaining Consent
Date
(Investigator or IRB Approved Designee)

_____

Witness to Consent Procedures (Optional unless IRB or Sponsor required)
Date

Revocation of consent form:

NOTE: **A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND, IF APPROPRIATE, A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD.**

FOR OFFICE USE ONLY:
STUDY APPROVED FOR ENROLLMENT OF: ___ Adults Only ___ Adults and Children ___ Children Only

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

(Objective-3)

TITLE: Ocular Photosensitivity Assessment among Refractive Surgery Eyes (LEC 09-19-321)

INVESTIGATOR: Asra Fatima

SITE: LV Prasad Eye Institute
LV Prasad Marg, Banjara Hills
Hyderabad - 500034 Telangana,
India.
Ph: +91-40-30612121

Introduction

This consent form describes a research study and describes what you may expect if you decide to participate. You are encouraged to read this consent form carefully and ask any questions you may have before making your decision. You can ask the person who is presenting this form any questions. You are being asked to take part in this study because you have been diagnosed with an ophthalmic (eye) problem or you have healthy eyes.

This form describes the known risks and benefits of taking part in this study. You are free to choose whether or not to participate in this study.

In this consent form, "you" always refers to the subject. If you are a legally authorised representative or parent, please remember that "you" refers to the study subject or your child.

Purpose of Study

This research project may improve our ability to understand, diagnose, or treat patients who undergo refractive surgery by measuring your visual light sensitivity threshold. Your participation is voluntary.

Study Procedures

If you agree to take part in this study, your involvement will allow us to look at your records and to perform eye tests on you. We will ask some questions about your medical history (onset of symptoms (if applicable), vision status, other health problems, etc.) and the history of your family (any relatives with major visual problems, etc.). We will use the information gathered during your general eye examination for this study.

-You will have a Photosensitivity test performed to test light sensitivity. You will sit in front of an instrument with a sequence of light bulbs. Light intensity is adjusted from a connected computer. The light will become brighter and you will be instructed to indicate at which intensity the light becomes uncomfortable by pressing a button on the table in front of you.

-You may be asked to fill out a questionnaire asking you questions about your health and vision

-You may have you visual acuity measured. This tests how well you see the letters on a chart at various distances. You will be asked to read the letters.

-You may have a full-eye exam. The doctor will examine your eyes through a microscope and take notes of what he sees.

-You will not receive a report from the study because the tests are done for research purposes only.

We may ask you to have up to 3 visits on different days. Testing sessions can be scheduled at a time convenient for you or may take place when you return for clinical follow-up visits.

Risk and Discomfort

There are no risks in having a photosensitivity test, refraction, visual acuity measurement, and questionnaire.

Benefits

Research is designed to benefit society by gaining new knowledge and may help replace invasive procedures with noninvasive tests. You may not benefit personally from being in this research study. You may benefit by assessing your sensitivity threshold values following treatment if you have light sensitivity.

Alternatives

You have the alternative not to participate in this study. You can decide to stop participating in this study at any time. Not participating in this study will not affect your medical care.

Cost

All study required and related activities, procedures, and examinations will be covered by the study.

Incentive/Payments to Participants

You will not be provided with any form of monetary compensation for the completion of each study visit.

Compensation for injury

You may be exposed to the risk of injury from participation in this study. If an injury occurs, treatment will be available free of cost for you.

Confidentiality

By signing this consent, you authorize the Investigator and his staff to access your medical records and associated information as may be necessary for purposes of this study. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The Investigator and his collaborators and staff will consider your records confidential to the extent permitted by law. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations. Finally, if you should seek treatment at L V Prasad Eye Institute, information from this study may be given to the treating physicians and other medical staff at L V Prasad Eye Institute. In turn, the treating physicians and other medical staff at L V Prasad Eye Institute may provide information about your treatment and care to the study investigators.

Voluntary Participation/Withdrawal from study

Your participation in this study is voluntary. You may refuse to participate, or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled.

This will not affect the medical care you receive from L V Prasad Eye Institute. You must tell the study investigator if you wish to stop taking part in the study. Your participation in this study may be discontinued, without your consent, at any time by the study investigator, if he/she believes that participation in the study is no longer in your best interest. The Institutional Review Board (IRB), regulatory authorities, or the sponsor may also discontinue your participation in the study.

Student Rights If you are a student, your desire not to participate, or your request to withdraw from the study, will not affect your grades or other academic standing within the organisation.

Employee Rights If you are an employee of the organisation, your decision to participate in or withdraw from the study will not affect your employment within the organisation.

Questions

Study investigators will be happy to answer any questions that you may have regarding this study plan. You may call Asra Fatima at 7207299796 to have any questions regarding this study answered or if you feel you have suffered an injury related to the study. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

AGREEMENT OF DECISION TO PARTICIPATE

I have read this consent, which is printed in English (a language which I read and understand). This study has been explained to my satisfaction and all of my questions relating to the study procedures, risks and discomforts, and side effects have been answered. If I have any further questions regarding this study, or in the event of a study-related injury, I should contact the appropriate person named above. Based on this information, I voluntarily agree for me/my child to take part in this study.

Signature of Participant Date

Printed Name of Participant

Signature of Parent/Legally Acceptable Representative Date

Printed Name of Parent/Legally Acceptable Representative

Printed Name of Child (if applicable)

Signature of Person Obtaining Consent Date

Printed Name of Person Obtaining Consent

Revocation of consent form:

APPENDIX-E PLAGIARISM REPORT

Tear Film changes and Predictive factors of Symptomatic Dry Eyes and Visual Light Sensitivity after Laser Refractive Surgery

by Asra Fatima

Dr. Kerida V. Nagaraju
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Tear Film changes and Predictive factors of Symptomatic Dry Eyes and Visual Light Sensitivity after Laser Refractive Surgery

ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Asra Fatima, Pavani Vadla, Nagaraju Konda. "Changes in the tear film and meibomian gland morphology between preclinical dry eye and normal subjects represented by ocular surface disease index scores", Experimental Eye Research, 2022 Publication	21%
2	www.science.gov Internet Source	<1%
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This manuscript is by Ms. Asra Fatima
Therefore, 21% similarity is accepted from 25%.

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Assistant Professor
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University of Hyderabad
Hyderabad, Telangana, India

	patients with dry eye", Clinical and Translational Science, 2022 Publication	
6	"Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3", Springer Science and Business Media LLC, 2002 Publication	<1 %
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12	Kraig S. Bower, Rose K. Sia, Denise S. Ryan, Michael J. Mines, Darlene A. Dartt. "Chronic dry eye in photorefractive keratectomy and laser in situ keratomileusis: Manifestations, incidence, and predictive factors", Journal of Cataract & Refractive Surgery, 2015	<1 %

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