"EVALUATION OF TEAR FUNCTION AND OCULAR SURFACE CHANGES IN PATIENTS WITH PSEUDOEXFOLIATION"

By

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Dissertation submitted to the

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, TAMAKA, KOLAR

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY IN OPHTHALMOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS

SL NO.	ABBREVIATION	FULL FORM
1.	ADDE	Aqueous Tear-Deficient Dry Eye
2.	DEWS	Dry Eye Workshop
3.	DED	Dry Eye Diseases
4.	KCS	Keratoconjunctivitis Sicca
5.	MGD	Meibomian Gland Dysfunction
6.	NC	Normal Cytology
7.	OSDI	Ocular Surface Disease Index
8.	PAS	Periodic Acid Schiff
9.	HIV/HTLV1,	Anterior Chamber
10.	LOXL1	Lysyl Oxidase Like 1 Gene
11.	PXG	Pseudoexfoliative Glaucoma
12.	LFU	Lacrimal Function Unit
13.	TMH	Tear Meniscus Height
14.	TBUT	Tear Film Breakup Time
15.	LOH	Loss Of Heterozygosity
16.	ACD	Anterior Chamber Depth
17.	SS	Sjogren Syndrome
18.	KCS	Keratoconjunctivitis Sicca
19.	RE	Right Eye
20.	LE	Left Eye
21.	LASIK	Laser In Situ Keratomileusis
22.	MGD	Meibomian Gland Dysfunction
23.	OSDI	Ocular Surface Disease Index
24.	SSDE	Sjogren Syndrome Dry Eye
25.	PAS	Periodic Acid Schiff
26.	ST	Schirmer's Test.
27.	CIC	Conjunctival Impression Cytology

28.	NEI-VFQ25	National Eye Institute Visual Function Questionnaire 25
29.	MAP kinases	Mitogen Activated Protein Kinase
30.	PC	Posterior Chamber
31.	POAG	Primary Open Angle Glaucoma
32.	GF	Growth Factors
33.	PAN	Poly Arteritis Nodosa
34.	SLE	Systemic Lupus Erythematosus
35.	WG	Wegener's Granulomatosis

ABSTRACT

PURPOSE

Dry eye disease is a multifactorial disease of the ocular surface, which results in symptoms of discomfort, visual disturbances and tear film instability, due to ocular surface damage. Elderly age groups are more prone to dry eye illness. Dry eye prevalence increased among those over 70 years old by up to 36.1%. PEX syndrome is a common age-related condition, characterised by accumulation and deposition of white fluffy amyloid like proteinaceous material. Ocular manifestations of PEX syndrome include dry eye disease, open angle glaucoma, and cataract. Thus, we intend to take up the study to determine association between ocular surface changes in patients with PEX syndrome in Kolar district. This is the first study conducted in the Kolar district, to assess the association between ocular surface changes in patients with PEX syndrome.

AIMS AND OBJECTIVES

1. To study tear film stability by:
   a. Tear meniscus height
   b. Schirmer's test 1 & 2
   c. Tear breakup time
2. To assess and grade the ocular surface changes using fluorescein staining and conjunctival impression cytology
3. Subjective assessment of ocular symptoms using "Ocular Surface Disease Index" questionnaire

MATERIAL AND METHODS

This cross-sectional study will be conducted on a minimum of 45 patients fulfilling the inclusion criteria in the department of Ophthalmology, R. L. Jalappa Hospital and Research centre, Kolar from January 2021 to June 2022.

RESULTS

- In our study the majority of patients with pseudoexfoliation were of >70 years. In our present study females 23(51.1%) are more than males 22(48.9%). According to Grading of dry eye, in the right eye, 20(44.4%) were moderate grade, 12(26.7%) were mild grade, 7(15.6%) were severe grade and 6(13.3%) were normal grade. In Left eye, 21(46.7%) were moderate grade, 12(26.7%) were mild grade, 6(13.3%) were severe grade and 6(13.3%) were normal grade. CIC, fluorescein staining, TBUT, Schirmer's tests I and II, and TMH, all showed a statistically significant results with dry eye in the current study.

CONCLUSION

Patients with pseudoexfoliation syndrome are more likely to have dry eyes because these patients have uneven tear films and fewer goblet cells, which may be seen with cytology of the conjunctival impression and tear film tests.

KEY WORDS- PSEUDOEXFOLIATION SYNDROME, SCHIRMER'S TEST, TBUT, OSDI, DRY EYE SEVERITY GRADE, CONJUNCTIVAL IMPRESSION CYTOLOGY.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOS

INTRODUCTION

1. INTRODUCTION

Pseudoexfoliation(PEX) syndrome is clinically a generalized fibrillopathy characterized by accumulation of abnormal elastic fibrillar material in intraocular and extraocular tissue.[1] 10% of people over the age of 60 years have pseudoexfoliation syndrome, a prevalent age-related disorder that is marked by the accumulation and deposition of white, fluffy proteinaceous material with an amyloid-like appearance.[2] In the eye it is present in the anterior chamber and its angle, corneal endothelium, trabecular meshwork, epithelium of the ciliary body, iris, lens and conjunctiva. The extraocular deposition is seen in skin, lungs, myocardium, liver, kidney and cerebral meninges.[3,4]

Ocular manifestations of PEX include dry eye disease, open angle glaucoma, and cataract. It also affects the dilation of pupil, causes raised IOP and intraoperative complications such as vitreous loss and subluxation of lens.[5]

Pseudoexfoliation results in the instability of the tear film and dry eyes, because the accessory lacrimal glands and goblet cells that make up PEX material accumulate near the conjunctiva.[6]

As per "INTERNATIONAL DRY EYE WORKSHOPS CLASSIFICATION, defined dry eye syndrome as a "Multifactorial disease of tears and ocular surface that results in feelings of discomfort, visual impairment, and tear film instability with potential damage to the ocular surface".[7]

Dry eye is a common eye disorder characterized by the inadequate synthesis of tear film to moisturize the ocular surface. The prevalence of dry eye increases as age advances and it varies from 5 to 50% globally.[8,9] Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation, damage, and neurosensory abnormalities play etiological roles.[10]

This condition causes a common ocular surface inflammatory disease that significantly affects the quality of life, due to dysfunction of the lacrimal function unit, resulting in chronic inflammation and tissue damage.[8]

Dry eye may be classified into two groups 1) Dry eye with reduced tear production (aqueous-deficient) and Dry eye with increased evaporation of the tear film (hyper-evaporative) or a combination of the two. [11]

10% of dry eye patients also have an aqueous-deficient disease. The combined effects of hyper evaporative and aqueous diseases account for about 80% of people with dry eye.[12] Patients with tear malfunction frequently report stinging, blurring, foreign body sensation, blurred to persistent eye discomfort, photophobia, and fluctuating vision. Patients who experience chronic eye discomfort may have a lower quality of life.[12]

The risk factors associated with dry eye includes large incision cataract surgery, penetrating keratoplasty, contact lens users, cigarette smoking, collagen vascular disease, irradiation, old age groups.[13,14]Menopause, LASIK and refractive excimer laser surgery, hematopoietic stem cell transplantation, hepatitis C, beta-blockers, diuretics, diabetes mellitus, radiation therapy, low humidity environment, sarcoidosis, ovarian dysfunction, alcohol use, oral contraceptives, and pregnancy are additional causes of dry eyes.[12]

Dry eye disease is a reversible condition, if diagnosed early or else it may lead to complications like: Corneal Abrasion, Recurrent Inflammations, Keratitis, Corneal Perforation, Corneal Scarring, Irreversible Visual Impairment.

Clinical diagnosis of dry eye is mostly focused on symptom analysis because DED cannot be detected with a specific test.[15]

Despite the fact that dry eye is diagnosed solely on symptoms, it is crucial to evaluate the ocular surface using clinical testing and histological techniques.

The clinical diagnosis of dry eye is based on slit lamp examination, Schirmer's test, Tear Meniscus Height (TMH), Tear Film Breakup Time (TBUT), and fluorescein staining. Histopathological diagnosis by conjunctival impression cytology. Patients with pseudoexfoliation syndrome are more likely to develop dry eye disease.

Thus, we intend to take up this study in our setup to determine the association between tear function and ocular surface changes in patients with pseudoexfoliation syndrome in the Kolar district.

AIMS &

OBJECTIVES

2. OBJECTIVES OF THE STUDY

1. To study tear film stability by:
   a. Tear meniscus height (TMH)
   b. Schirmer's test 1 & 2
   c. Tear breakup time (TBUT)
2. To assess and grade the ocular surface damage using fluorescein staining and conjunctival impression cytology
3. Subjective assessment of ocular symptoms using "Ocular Surface Disease Index" (OSDI) questionnaire

REVIEW OF LITERATURE

3.REVIEW OF LITERATURE

HISTORY:

In 1917, Lindberg[16] described greyish or bluish flakes of material on the pupillary border in some patients with glaucoma. **Vogt**[17] later introduced the term "senile exfoliation of the lens capsule" and postulated that this material indicated degenerative alterations of the lens capsule followed by secondary desquamation.

Busacca[18] suggested that the exfoliative material didn't indicate lens capsule degeneration, but rather the deposition of material generated elsewhere in the eye. After demonstrating that exfoliative material was histochemically distinct from the lens capsule, Dvorak-Theobald[19] proposed the name pseudoexfoliation of the lens capsule to distinguish this situation from real exfoliation of the lens capsule caused by infrared radiation. This disease directly damaged the anterior lens capsule, according to later electron microscopic studies by Ashton[20] and collaborators and Bertelsen[21] and colleagues. The term "fibrillopathia epitheliocapsularis" is suggested by Bertelsen and colleagues, who suggest that pre-equatorial lens epithelial cells formed the abnormal fibrillar material.

The condition is known as "basement membrane exfoliation syndrome" according to Eagle and colleagues[22], who think the material exhibited aberrant basement membrane secretions.

The terms exfoliation syndrome and PEX are now most commonly used to designate this disorder and are used interchangeably in current literature. However, since recent ultrastructural studies indicate that the material on the lens capsule is derived, at least in part, from the lens, it is proposed that the disorder be called exfoliation syndrome (PXF).[23,24]

Eagle and colleagues,[22] who believe that the material represented abnormal basement membrane secretions, have called this condition “basement membrane exfoliation syndrome”. The terms exfoliation syndrome and pseudoexfoliation syndrome are now most commonly used

to designate this disorder and are used interchangeably in current literature. However, since recent ultrastructural studies indicate that the material on the lens capsule is derived, at least in part, from the lens, it is proposed that the disorder be called exfoliation syndrome (PXF).[23,24]

EPIDEMIOLOGY:

The prevalence of pseudoexfoliation syndrome is worldwide. There has been a considerable range in the reported prevalence of pseudoexfoliation syndrome, both with and without glaucoma.

According to The Framingham Eye Study[25], 0.6% of Americans between the ages of 52 and 64 and 5% of Americans between the ages of 75 and 85 have pseudoexfoliation syndrome.

In India, the prevalence rates were 7.4% for Lamba and Giridhar[26] and 1.88 percent for Sood N.N. (1965). (1984). According to Aravind H et al., the prevalence rate in South India is 3.8%. (2003). A clinical examination may understate the true prevalence of pseudoexfoliation syndrome in a given group by as much as double. Because the pupil is not dilated or the lens is not tested with a slit lamp after the pupil has been dilated, many cases go undetected.

Age has an impact on prevalence; the disease commonly manifests between the ages of 60 and 70. Pseudoexfoliation Syndrome, however, may start in mid-adulthood but doesn't usually manifest itself till later in life.

Sex ratio reports are conflicting.

A hereditary transmission of Pseudoexfoliation Syndrome is not yet clarified.

Tarkkanen[29] (1962) suggested the presence of a gene bearing 3 characteristics:

a. An abnormality of the drainage channels of the aqueous

b. Pseudoexfoliation and

c. degeneration of the pigment epithelium of the iris.

Variations in the expressivity of this gene would explain why the three events are sometimes found.

Kelvin Y.C. Lee et al.[30] investigated PXF/PXG correlations with polymorphisms containing R141L, G153D, and introns found in the first exon of the LOXL1 on Chromosome 15q 21. Indians and other Asian ethnicities have reported connections between LOXL1 and PXE.

After researching six Icelandic families, each of which had at least one affected member, "R.R. Allingham" et al.[31] (2001) discovered that PEX is an inherited ailment that is passed down to the second generation through a mother who has the sickness.

Kozobolis et al [16] (1999) noted LOH in genetic loci in tissues involved in PEX which implies genetic role in the pathogenesis of pseudoexfoliation at cellular level.

Regarding the contribution of environmental factors on the emergence of pseudoexfoliation syndrome, there are no clear-cut data.

Pseudoexfoliation Syndrome is currently understood to be primarily a bilateral syndrome, with unilateral occurrences mainly representing an earlier stage of the condition's natural history.

- Bartholomew (1971) [32] has conveniently described PEX in stages:

a) Pregranular

b) Granular

This is the earliest sign occurring between 30-50 years and can be described in four stages for convenience.

1. **PREGRANULAR STAGE:**

a) **Stage I:**

- In this stage greyish, radial, thin, fusiform, non-granular striae around 80 in number are present on the middle third of the anterior capsule, variable in length and evenly distributed in all quadrants.

b) **Stage II:**

- As the initial stage develops, the striae get a little bit wider and closer together.
- The inner ends become blunt and broader, while the outer ends get a little bit longer.

c) **Stage III**:

- The striae broaden and the blunted inner ends begin to touch one another, thus forming a continuous dentate line.
- Even with high magnification there are no granular deposits visible.

d) **Stage IV**:

- Fine granular deposits appear in addition to the striae.
- The width of the outer band is caused by friction between the pupillary border and iris as they move against the capsule.

2) GRANULAR STAGE:

- Characterized by flaky, granular deposits on anterior lens capsule, pupillary margin, iris surface and crypts, floating in aqueous, corneal endothelium, ciliary body, zonules, trabecular meshwork and occasionally on vitreous face. [26]

CLINICAL FEATURES

1. OCULAR MANIFESTATIONS [33,34,35]

a) Lens and Zonules:

- The most accurate and crucial PEX diagnostic feature is deposition of powdery white debris on the lens surface anteriorly.
- The three distinct zones of PEX on lens are–

1. a central disc that is almost identical in size as the pupil and relatively homogeneous;
2. a granular, frequently layered periphery, and
3. a distinct space between the two.

The central zone is a uniform white coating that covers the anterior pole of the lens capsule. Its diameter ranges from 1.5 to 3 mm and is often a bit smaller than physiological pupil. It might be frosty white in the centre, with granular margins, and radial striations. It might be multilayered.On all sides, tongue-like extensions with curled edges surround the object's axis. The granularity of the peripheral layers is consistent with undisturbed accumulation of Pseudoexfoliation material. Deposits of white flaky material on the anterior lens surface are the most reliable and significant Pseudoexfoliation Syndrome diagnostic characteristic.

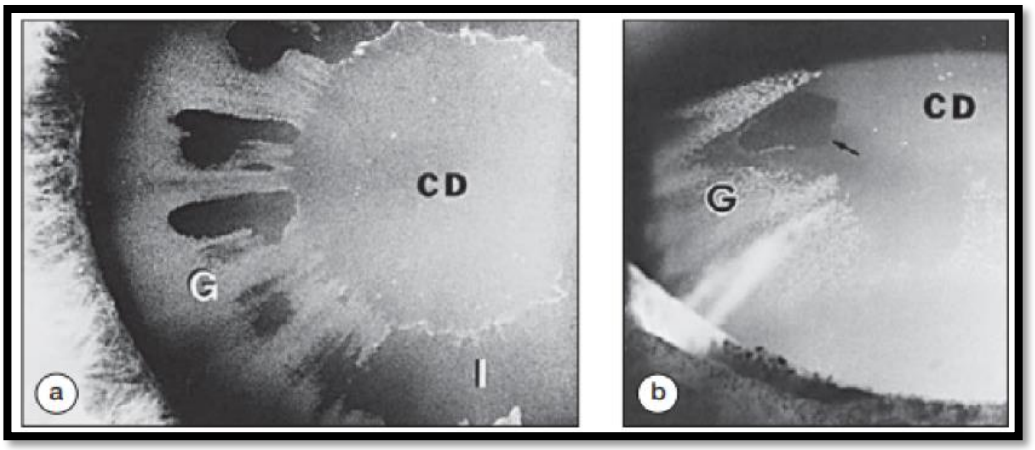


Figure 1. (a) PEX on the lens capsule

It is thought that a substance that would eventually cause PEX, first diffusely deposits itself on the lens surface.A very early (pre-capsular) stage may be indicated by the lens surface in one eye having a continuous "ground glass" or "matte" aspect in contrast to the other.The pre-capsular layer at this stage is ultrastructurally made up of micro-fibrils, in contrast to fully grown exfoliation fibrils.

The intermediate zone is formed when the iris rubs against the lens' surface during pupillary migration. Where PEX material is eliminated in the region that will eventually become the clear zone, faint clefts start to appear. These clefts develop throughout time and eventually converge.

The clinical classification of PEX:

1. **SUSPECT PSEUDOEXFOLIATION SYNDROME:**

- Early Pseudoexfoliation Syndrome (Electron Microscopy): Pre-capsular layer.
- The concealed or presumed pseudo exfoliation syndrome is indicated by posterior synechiae without a distinct cause.

2. **DEFINITE PSEUDOEXFOLIATION SYNDROME:**

- Focal anomalies, notably "supero-nasally," in the pre-capsular layer are a sign of the Mini-Pseudoexfoliation Syndrome.
- The classic pseudoexfoliation syndrome is in its late stages.

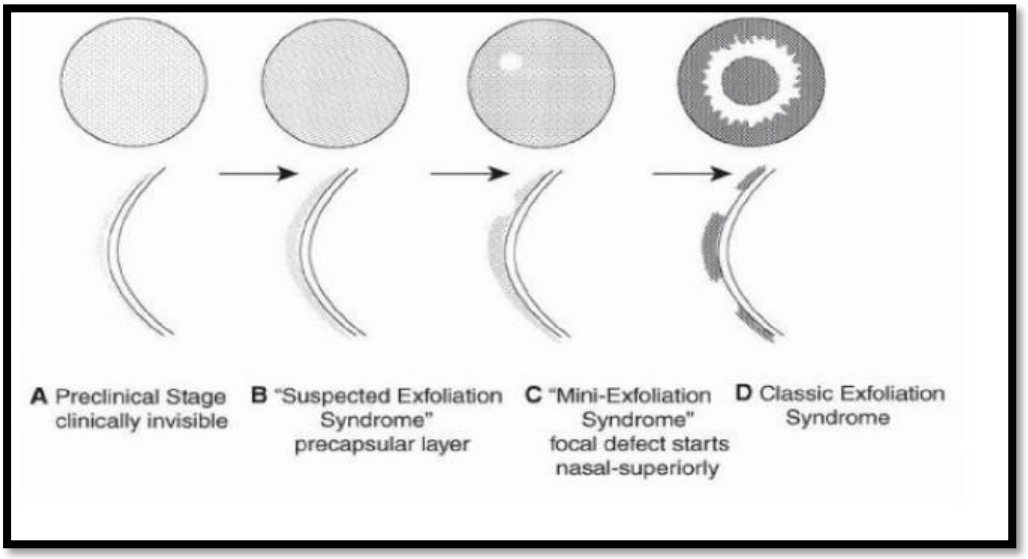


Figure 2 . Clinical classification of exfoliation syndrome.

Phacodonesis is frequent but isn't usually linked to iridodonesis, which may be caused by an increased iris rigidity. The possibility of spontaneous subluxation and lens dislocation exists; the likelihood of phacodonesis increases with the density of the pseudoexfoliation material. Inferiorly, lens dislocation is more frequent. Zonular fibrils that have been coated with various concentrations of pseudoexfoliation material strain and eventually rupture. The fibres gradually get thicker and shorter, eventually clumping irregularly on the lens surface.The fibres behind the equator are the first to break, whereas those immediately in front of the equator hold together the longest.

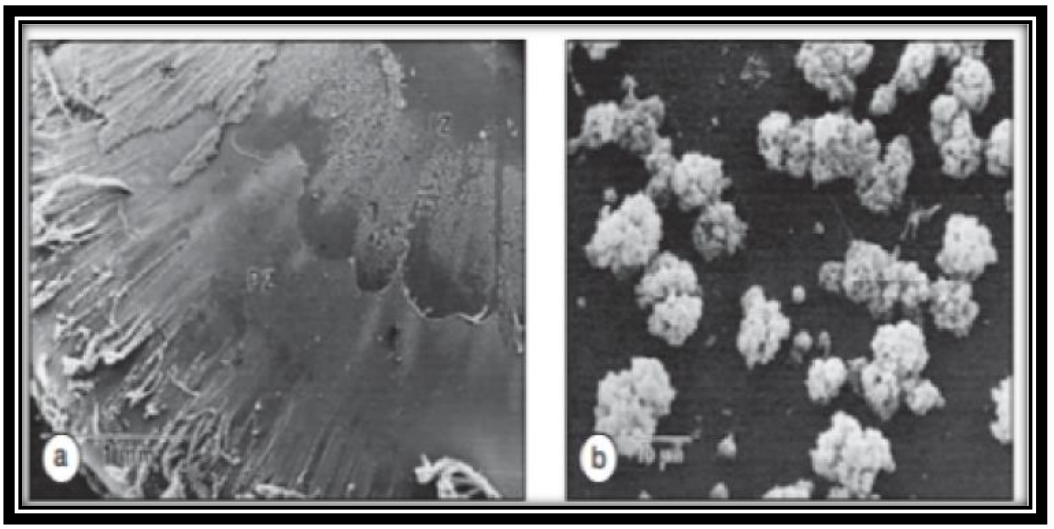


FIGURE 3. The anterior lens surface in exfoliation syndrome.

- Clinical and surgical complications arising from zonular instability are: [37-39]

a. Phacodonesis

b. Subluxation of lens

c. Pupillary /ciliary block causing angle closure glaucoma.

d. Vitreous loss

e. Zonular rupture or dehiscence during surgery

f. Posterior capsule rupture

g. Decentration of lens implant

h. Secondary cataract.

i. Pseudoexfoliation deposition on lens results in lens opacification, the most predominant type of cataract in PEX syndrome is nuclear cataract.

b) <u>Anterior chamber</u> [40,41]

Anterior chamber depth is smaller in eyes with PEX syndrome than in eyes without PEX syndrome. This is due to zonular weakness in PEX syndrome which causes the anterior movement and increased curvature of the lens. An AC depth of less than 2.5 mm centrally is

an indicator of zonular instability.

.**c) Iris and Pupil:**

The pupillary border, which is close to the lens, is where pseudoexfoliation material is most obvious. The substance makes the iris stiffer.

Pseudoexfoliation syndrome is defined by the pigment loss from the iris sphincter region and subsequent deposition on the anterior chamber structures. The substance of the lens causes the pigment epithelial cells of the iris to rupture at the sphincter and ruff areas, and pigment simultaneously diffuses into the anterior chamber. The trabecular pigmentation is increased, the pupillary ruff is lost, the iris's sphincter region is transillumed, and pigment is deposited on the iris's surface. Over the entire sphincter region, there may be extensive depigmentation visible as a diffuse "starry sky pattern" on transillumination or a "moth-eaten appearance". Pseudoexfoliation syndrome predisposes to the formation of synechiae between the iris pigment epithelium and the anterior lens capsule. Following surgery, it is more likely that posterior synechiae between the iris and intraocular lens may form. Iris hypoperfusion resulting in patchy neovascularization of the iris is one example of iris blood vessel abnormalities, along with vessel dropout with collateral development, obliterated or restricted lumens, considerable iris vasculature remodelling, and iris hypoperfusion.[34] Inflammation is more frequent after cataract surgery, and a transient fibrinoid reaction related to a damaged blood-aqueous barrier is feasible.[37] Intrastromal bleeding during mydriasis is a sign of vascular damage. Poor pupillary dilatation may be caused by atrophic alterations in the sphincter and dilator muscle tissues, presumably as a result of hypoxia, and the apparent weakening of muscle cells by pseudoexfoliation material. Following diagnostic mydriasis or surgery, melanin granule dispersion may be so severe that heterochromia iridium may develop. The degenerative alterations and cell membrane tears of the posterior pigmented epithelial cells brought on by

extracellular pseudoexfoliation material are related to the mechanism of melanin liberation. Marked intra-ocular pressure rise after mydriasis correlates with the amount of the pigment liberated.

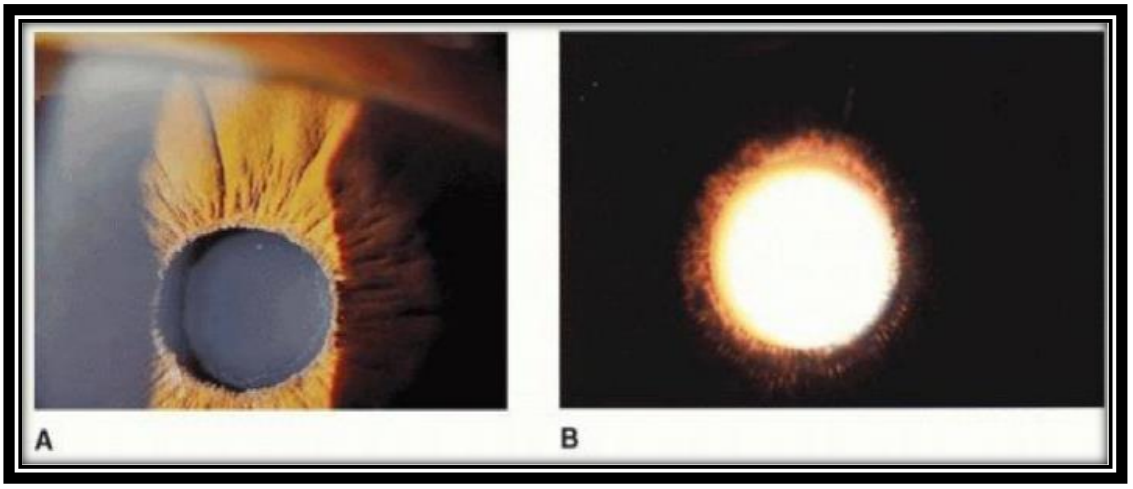


Figure 4. A: Exfoliative material at pupil border. B: Moth-eaten pattern of peripupillary transillumination defects.

d) Cilliary Body:

The cilliary processes were examined clinically by **Mizuno and Muroi**[38] with special type of Gonioscopy lens; almost all eyes with exfoliation showed accumulation of material on the zonules and cilliary body.

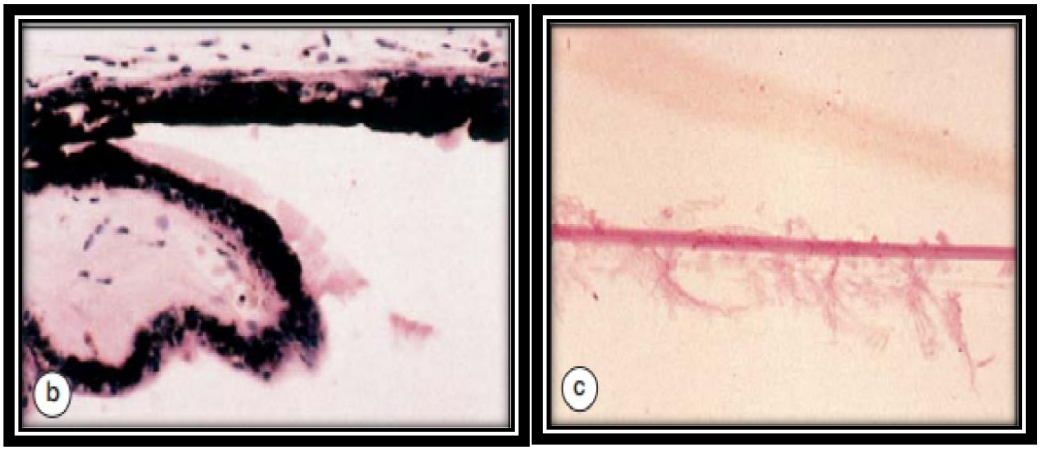


Figure 5. (b) Ciliary process in exfoliation syndrome. **(c) Zonular fiber** coated with exfoliative material.

e) Glaucoma and Pseudoexfoliation Syndrome: [37,38]

Open-Angle Glaucoma :

- While the existence of association between Pseudoexfoliation Syndrome and Open Angle Glaucoma has been well known, the mechanisms are still not clarified.
- The possible mechanism of glaucoma in pseudoexfoliation syndrome :

a) There is an increase in the aqueous outflow resistance probably due to trabecular cell dysfunction,

b) Blockage of meshwork by Pseudoexfoliation Syndrome liberated pigment and

c) concomitant primary open angle glaucoma.

Glaucoma and a high IOP are present in 20% of patients with PEX at the time of diagnosis. Patients with PXF who do not have glaucoma should be thought of as being susceptible to the disease because 15% of them see a rise in IOP within ten years. This highlights the importance of meticulous follow-up in patients with pseudoexfoliation syndrome

Angle-Closure Glaucoma :

- Angle closure glaucoma is more likely to occur in eyes with pseudoexfoliation syndrome due to a number of factors.
- Causes of pupillary block:

1. Increased iris thickness or rigidity
2. Anterior lens movement secondary to zonular weakness or dialysis.
3. Posterior synechiae caused by degeneration of the sphincter muscle and increased adhesiveness of the iris to the lens.

f) Angle Characteristics: [38]

Aqueous in the posterior chamber causes the iris root, which is the weakest part of the iris, to expand. This encourages the creation of localised iris bombes, which obstruct the angle and give the iris a more rigid appearance than usual on gonioscopy.

Increased trabecular pigmentation is a prominent symptom that almost all people with clinically obvious illness have.It is an early diagnostic symptom that develops before the anterior lens capsule and pupillary margin show evidence of pseudoexfoliation material. It thickens in the affected eye and develops worse in eyes with pseudoexfoliative glaucoma.

Increased intraocular pressure is correlated with a greater degree of pigmentation. Sampolesi's Line, or pigment on Schwalbe's line, is a wavy line that is also an early symptom of pseudoexfoliation syndrome.

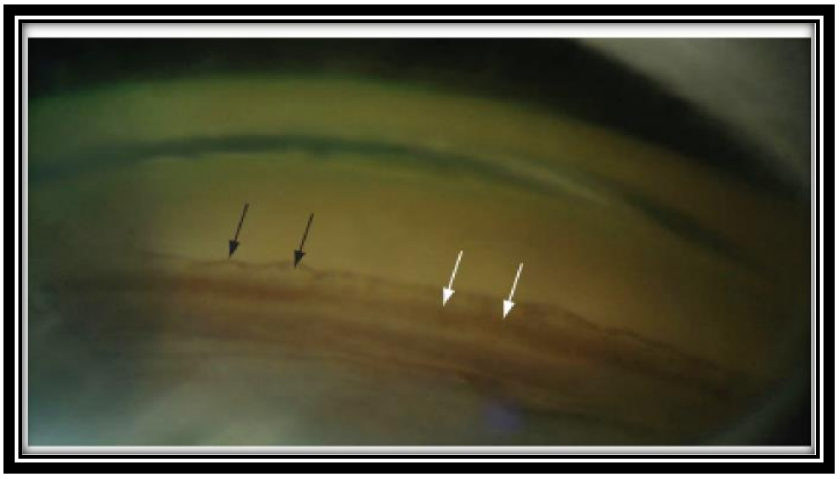


FIGURE 6. Goniophotograph of the anterior chamber angle in pseudoexfoliation syndrome: shows the Sampaolesi line (black arrows).

g) Vitreous:

Since hyaluronic acid and the substance that causes pseudoexfoliation are both acid mucopolysaccharides, vitreous alterations frequently go hand in hand with pseudoexfoliation

syndrome.In Pseudoexfoliation Syndrome, a change in water composition could disrupt hyalocyte metabolism, impairing the formation of hyaluronic acid and causing liquefaction.

h) Conjunctiva and Cornea:

Clinically, the conjunctiva appears healthy. Fluorescent angiography, however, indicates areas of neovascularization, clogged anterior cilliary veins, and the lack of the usual limbal vascular pattern.Specular microscopy indicates significantly decreased endothelial cell density even with normal intraocular pressure, as well as morphological changes in the size and shape of the endothelial cells in both the affected and unaffected colleague eyes. The pseudoexfoliation material may appear as solitary flakes on the endothelial surface of the cornea. The degree of pigment dispersion is related to a decline in endothelial cell density.

The increased central corneal thickness indicates early corneal impairment. These modifications may aid in early diagnosis and pre-operative evaluation before cataract removal.

2. SYSTEMIC MANIFESTATIONS [39,40]

Pseudoexfoliation material has been discovered in a number of organs, including the skin, lungs, gallbladder, liver, heart, kidney, bladder, and meninges. Ultrastructural examinations on eyes performed during autopsy imply that pseudoexfoliation syndrome is a multisystem condition.These tissues are positive for elastin and human amyloid P protein, and their staining patterns resemble those of tissues present in the eye.These findings support the idea that pseudoexfoliation syndrome, which is characterised by abnormal connective tissue metabolism throughout the body, has a systemic basis. Patients with pseudoexfoliation syndrome are found to have sensorineural-deafness.

THEORIES ON ORIGIN OF PSEUDOEXFOLIATION MATERIAL:

1. BASEMENT MEMBRANE THEORY:

There is strong evidence that the extracellular matrix problem known as pseudoexfoliation syndrome is characterised by an excessive synthesis or faulty breakdown of substances related to cell surfaces. After careful examination with an electron microscope, it was observed that the pseudoexfoliation material originated from the lens capsule, iris, cilliary body, and mucous membrane of the conjunctiva. Schlotzer- Schrehardt et al. showed systemic involvement of the viscera by pseudoexfoliation material using transmission electron microscopy in 1992. Typical The phrase "pseudoexfoliation syndrome" describes the finding of pseudoexfoliation fibres in tissue samples taken from organs other than the usual intraocular locations, including as the skin, heart, lungs, liver, kidney, and cerebral meninges. Using the indirect immunoperoxidase technique, Harnisch et al.[41] reported in 1981 that the fibrils included a basement membrane proteoglycan. This finding suggests that the generation of the exfoliation material may be related to a disrupted metabolism of the basement membrane.

2. ELASTIC MICRO-FIBRAL THEORY

Due to the immunological relationship between exfoliation material and elastic tissue, Li and colleagues hypothesised in 1989 that exfoliation fibres include peripheral Amyloid P protein binding sites similar to those seen on ordinary elastic fibres. The zonular elastic microfibrils and the exfoliation material have similar histochemical and antigenic characteristics.

In 1984, Garner and Alexander[42] postulated that the exfoliation fibrils might contain oxytalan, a microfibrillar component of elastic tissue seen in the body in places of mechanical stress.

Streeten et al.[43] discovered histochemical links between pseudoexfoliation material and zonular elastic micro-fibrils in 1987. In a ground substance, they also discovered similarities between

larger oxytalan microfibrils and zonular microfibrils.

The authors hypothesised that pseudoexfoliation fibres themselves might represent a kind of elastosis, presumably originating from aberrant aggregation of components related to elastic micro-fibrils, given the strong anatomic correlation between pseudoexfoliation fibres and elastosis in conjunctival specimens. In 1998, Schlotzer-Schrehardt et al.[44] used electron microscopy to study the matrix of the pseudoexfoliation material and demonstrated that it contained fibrilin-positive fibres, supporting the elastic micro fibril theory of its creation.

3. AMYLOID THEORY

Repo L.P. Naucharinen et al.[45] studied 13 biopsy specimens of iris tissue from individuals with pseudoexfoliation syndrome after cataract surgery in 1996 using light and electron microscopy. They demonstrated the relationship between miosis and degenerative changes in stromal tissue and the muscle layers of the iris, as well as the relationship between pseudoexfoliation material and amyloid in some eyes.Tsukahara and Matsuo[46] documented patients who had exfoliation as well as primary familial amyloidosis.

4. LYSOZOMAL THEORY

Mizuno et al.[47] discovery of strong acid phosphatase activity in histochemistry in 1980 demonstrated the role of lysosomes in the synthesis of exfoliation material. Lysosomal involvement could be explained by the potential rupture of pigment epithelial cells. The lysosomal proteolytic enzymes may facilitate granular disintegration. In 1982, Baba[48] showed that exfoliation material contained lipoprotein and postulated that this finding might be related to the enhanced permeability of the arteries in the anterior portion. He also discovered that the substance was a sulfated glycosaminoglycan, which made him believe that aberrant

glycosaminoglycan metabolism had first created the chemical. Heparin sulphate, chondroitin sulphate proteoglycans, laminin, entactin/nidogen, fibronectin, and amyloid P protein have all been identified by immunochemical study as being essential components of exfoliation material. The only type IV collagen between the surface of the capsular layer and the normal exfoliation material is a very thin layer. Type IV collagen's facilitating role in cell attachment and its probable role in the exfoliation material's adherence to the anterior central capsule.

The addition of elastin epitopes suggests that the exfoliation material is a multi-component expression of a disordered extracellular matrix formation, which comprises the main non-collagenous basement membrane components. The substantial labelling of exfoliation material for chondroitin sulphate demonstrates that an excessive and abnormal synthesis of glycosaminoglycans is one of the main changes in this sickness. Exfoliation material contains Type IV collagen and elastin epitopes, but does not completely replicate genuine basement membrane material as a result of these variables. High resolution scanning and transmission electron microscopy have both demonstrated that keratan and dermatan sulphate are present in the pseudoexfoliation material. No histochemical or enzymatic study has been able to pinpoint the precise origin of the pseudoexfoliation material. This along with the increased chances of surgical complications continues to arouse great interest in PEX syndrome.

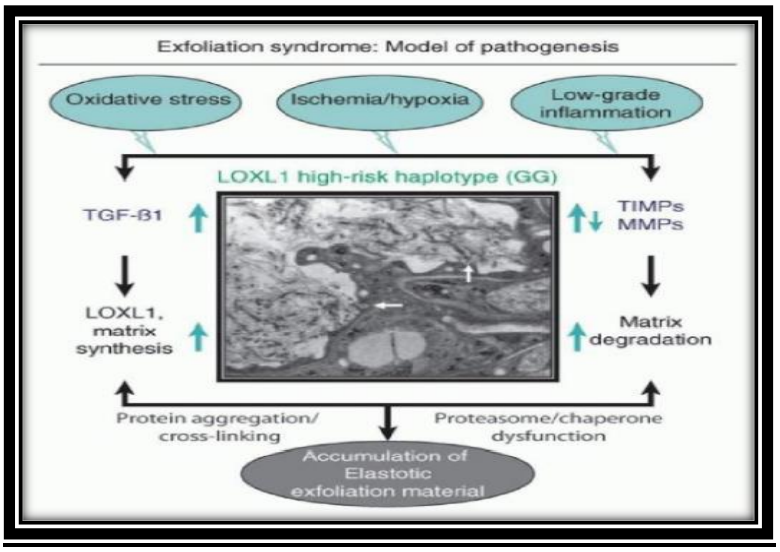


Figure 7. Exfoliation syndrome pathogenesis

STRUCTURE OF PSEUDOEXFOLIATION MATERIAL:

The Pseudoexfoliation Material consists of an irregular meshwork of randomly oriented cross-banded fibrils measuring about 30 nm in diameter within a loose fibro-granular matrix containing 6-10 nm micro fibrils. Davanger[49,50] stated that the fibrils were made up of a polysaccharide side chain encircling a protein core. Lateral filament aggregations give rise to fibrils. On light microscopy, the abnormally generated pseudoexfoliation material appears as a nodular or feathery aggregation that is PAS positive and eosinophilic brush-like. Electron microscopy images reveal that these aggregates are made up of an amorphous tangle of fibrils.The fibrils are intermingled with normal micro-fibrils and are embedded in an amorphous inter-fibrillar ground substance, most probably glycosaminoglycans. The extra-ocular Pseudoexfoliation Material is similar except that there is more matrix and less distinct banding pattern.

DRY EYE

HISTORY:

In 1995, National Eye Institute/industry workshop was conducted and Consensus developed on definition, diagnosis and treatment.[51]The International Task Force-DELPHI consensus panel on Dysfunctional Tear Syndrome was held between 2004 and 2006, and for the first time, a suggested level approach to treating dry eye disease was developed.[52]The definition of DES was updated in the 2007 Report of the International Dry Eye Workshop's Definition and Classification Subcommittee.[53]A Meibomian Gland Dysfunction International Workshop was held in 2011 and provided details on the pathophysiology and treatment of MGD.[54]

In order to link clinical and cytological findings related to dry eye syndromes, Mocanu CL conducted a study on impression cytology in the sicca syndrome in 2016. He concluded that Impression cytology is simple to use and quickly identifies tear film changes with high specificity and sensitivity.[55]

ANATOMY:

OCULAR SURFACE- includes cornea, conjunctiva, accessory lacrimal and meibomian glands.[56]

LACRIMAL FUNCTIONAL UNIT(LFU)-

- The eyelids, ocular surface, and lacrimal glands make up the lacrimal functional unit (LFU), together with the sensory and motor neurons that connect these parts.

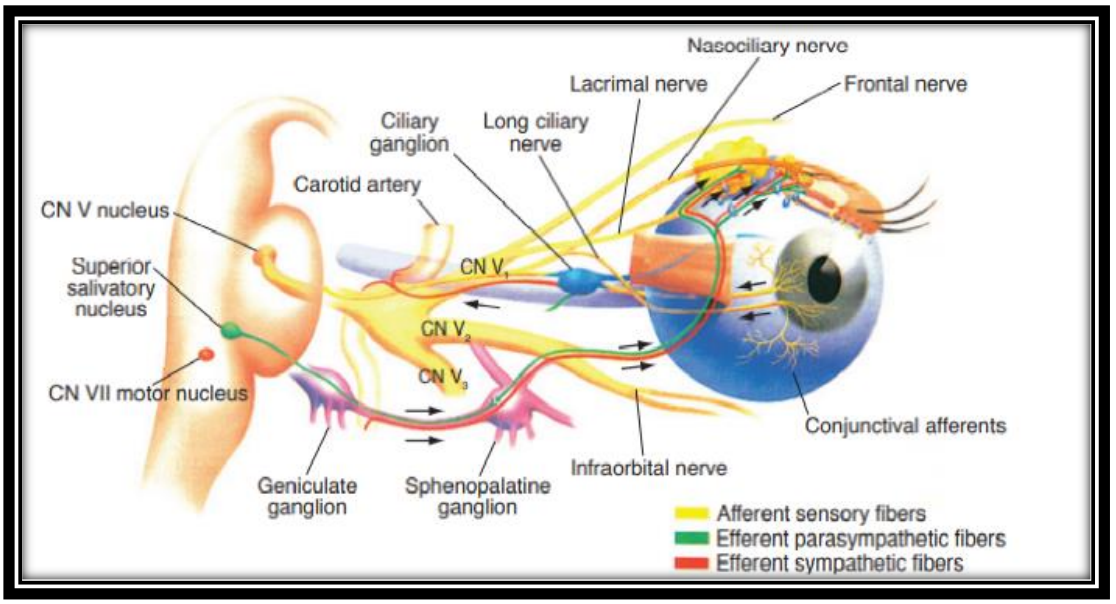


FIGURE 8. Lacrimal functional unit

The afferent component of the LFU is mediated through ocular surface and trigeminal nociceptors, which synapse with the efferent nerves (autonomic and motor nerves) in the brainstem.

TEAR FILM CONSTITUENTS

- The tear film has three layers**:**

1. Lipid layer secreted by the meibomian glands.
2. Aqueous layer secreted by the lacrimal glands.

3. Mucous layer secreted principally by conjunctival goblet cells..

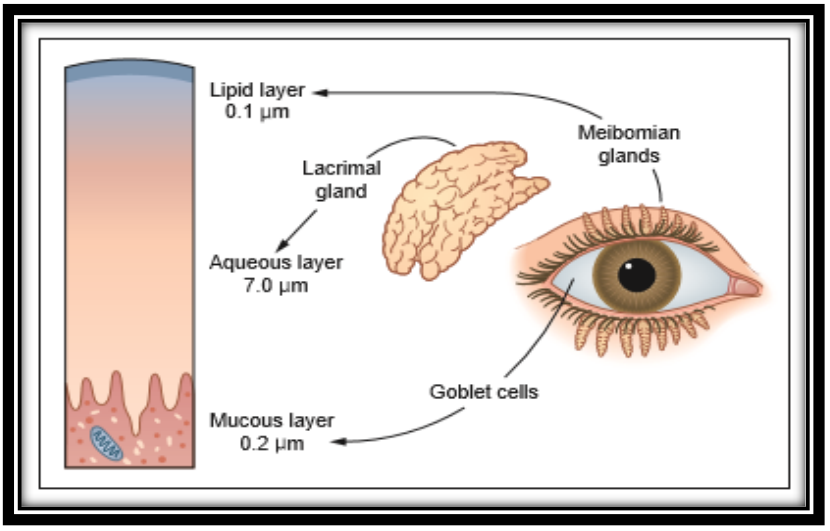


FIGURE 9: The three layers of the tear film

1. LIPID LAYER

Composition

The outer lipid layer is composed of a polar phase containing phospholipids adjacent to the aqueous-mucin phase and a non-polar phase containing waxes, cholesterol esters and triglycerides.The polar lipids are bound to lipocalins within the aqueous layer. During blinking, the lid moves, which helps the glands release lipids. Forced blinking can make the layer thicker, whereas infrequent blinking can make it thinner.

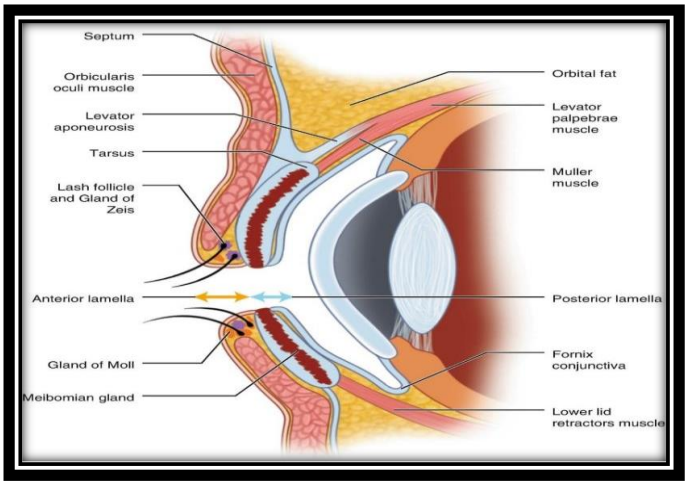


Figure 10. Organs associated with lipid discharge [Meibomian glands, Glands of Moll and Zeis]

Functions:

- To prevent evaporation of the aqueous layer and maintain tear film thickness.
- To act as a surfactant allowing spread of the tear film.
- Deficiency results in evaporative dry eye.

2.AQUEOUS LAYER [56]

SECRETION

The primary lacrimal glands produce around 95% of the aqueous component of tears, with the Krause and Wolfring auxiliary lacrimal glands producing the remaining 5%. Tear secretion has both fundamental (resting) and significant reflex components. The latter is controlled by the fifth cranial nerve and happens in response to sensory stimulation of the corneal and conjunctival tissues, tear breakdown, and ocular inflammation. Topical anaesthesia lowers it, and it decreases while you're sleeping. In reaction to injury, secretion can rise by 500%.

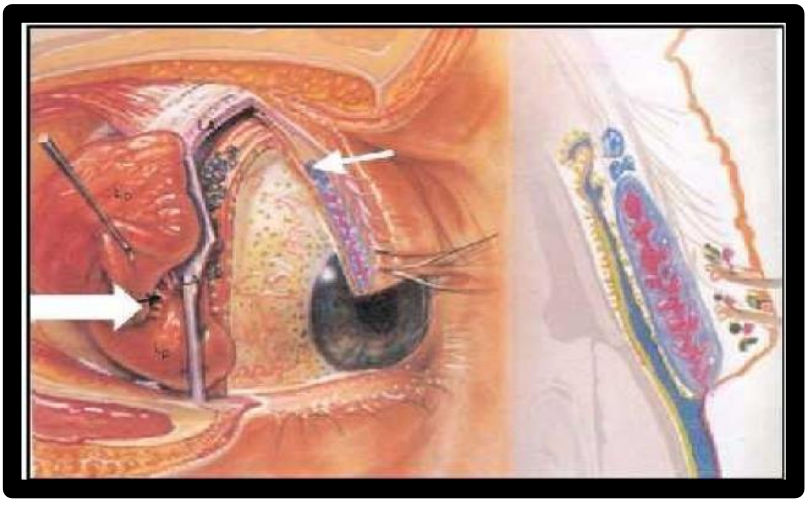


Figure 11. Organs associated with Aqueous tears emission [Lacrimal Gland (thick bolt), Glands of Krause (slim bolt), Glands of Wolfring (slim bolt)]

COMPOSITION

- Water, electrolytes, dissolved mucins and proteins.
- Growth factors derived from the lacrimal gland, the production of which increases in response to injury.
- Proinflammatory IL, cytokines that accumulate during sleep when tear production is reduced.

FUNCTIONS

- To provide atmospheric oxygen to the corneal epithelium.
- Antibacterial activity due to proteins such as IgA, lysozyme and lactoferrin.
- To wash away debris and noxious stimuli and facilitate the transport of leukocytes after injury.
- To optically enhance the corneal surface by abolishing minute irregularities.

3.MUCOUS LAYER

COMPOSITION

High molecular weight glycoproteins known as mucins can be either secretory or transmembrane in nature.Soluble or gel-forming are further classifications for "secretory mucins". They are predominantly synthesized by the conjunctival goblet cells and lacrimal glands. Transmembrane mucins are predominantly produced by the cornea's and conjunctiva's superficial epithelial cells, which are what make up its glycocalyx (extracellular coating).

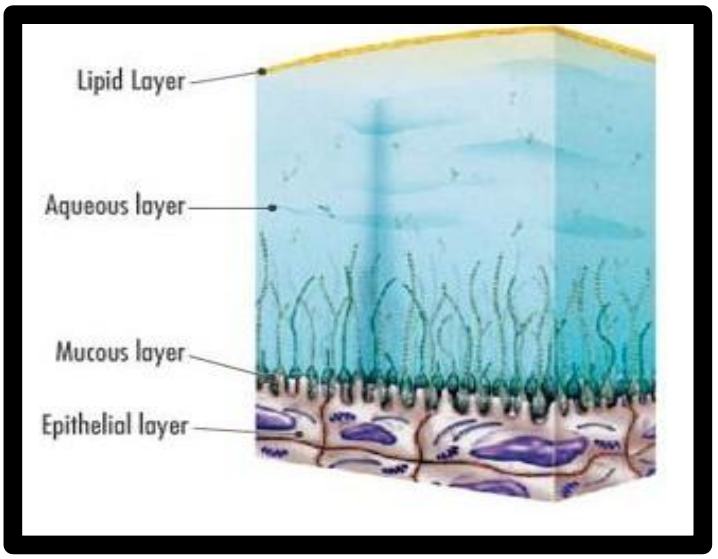


Figure 12. The Schematic representation of tear film**.**

FUNCTIONS

- To permit wetting by converting the corneal epithelium from a hydrophobic to a hydrophilic surface.
- Deficiency of the mucous layer may be a feature of both aqueous deficiency and evaporative states. Goblet cell loss occurs with cicatrizing conjunctivitis, vitamin A deficiency, chemical burns and toxicity from medications.

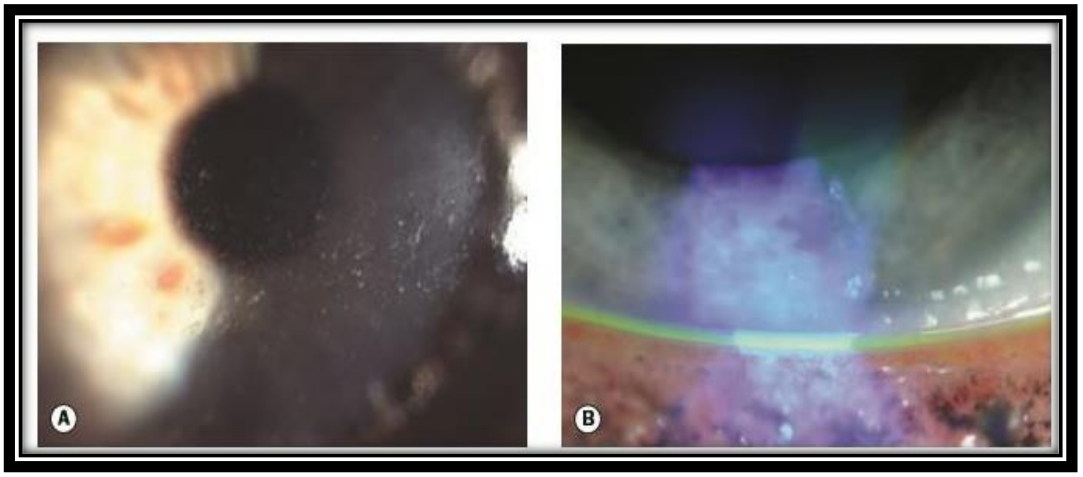


Figure 13. Tear film abnormalities in dry eye. (A) Mucous debris: (B) thin marginal tear meniscus.

Regulation of tear film components

- Hormonal**:** Androgens are the prime hormones responsible for regulation of lipid production.
- Oestrogens and progesterone receptors in the conjunctiva and the lacrimal glands are essential for the normal function of these tissues.

SPREAD OF THE TEAR FILM[56]

The tear film is mechanically dispersed across the ocular surface by a neuronally regulated blinking mechanism. Three factors are necessary for the tear film to effectively resurface:

1. Normal blink reflex.
2. Contact between the external ocular surface and the eyelids.
3. Normal corneal epithelium.

Table 1: Tear film origins, components and functions[56]

Tear Layer	Origin	Components	Physiological Functions
Lipid layer	Meibomian glands, accessory lacrimal glands	Wax, cholesterol, fatty acid esters	Lubrication, prevention of evaporation, stabilization
Aqueous layer	Lacrimal gland, accessory lacrimal glands	Water, electrolytes (Na^+, K^+Cl^-, HCO_3^-, Mg^{2+}), proteins (albumin, lysozyme, lactoferrin, transferrin, ceruloplasmin), immunoglobulins (IgA, IgG, IgE, IgM), cytokines, growth factors (EGF, TGF-α, TGF-β1, TGF-β2, bFGF, HGF, VEGF, substance P), others (glucose, vitamins)	Lubrication, antimicrobial, bacteriostasis, supply of oxygen and nutrients, mechanical clearance, regulation of cellular functions
Mucinous layer	Conjunctival goblet cells, conjunctival epithelial cells, corneal epithelial cells	Sulfomucin, cyalomucin, MUC1, MUC4, MUC5AC	Lowering of surface tension, stabilization of aqueous layer

	TEARS	PLASMA
1)water	98.2g%	94g%
2)solids, total	**1.8%**	**6g%**
3)Na+	142meq/l	137-142meq/l
4)K+	**15-29meq/l**	**5meq/l**
5)Cl-	**120-135meq/l**	**102meq/l**
6)HCO3-	26meq/l	24.3meq/l
7)Ca2+	2.29mg/100ml	
8)Glucose	*3-10mg/100ml*	*80-90mg/100ml*
9)Total proteins	*0.6-2gm/100ml*	*6.78g/100ml*
10)Aminoacids	8gm/100ml	
11)Urea	*0.04mg/100ml*	*20-40mg/100ml*

Table 2: Tear Film composition in comparison with blood Plasma

FUNCTIONS[56]

It forms a smooth ocular surface for optical clarity by filling in small surface irregularities in the corneal epithelium. It serves to keep the cornea and conjunctiva moist. It lubricates the preocular surface to facilitate eyelid blink by decreasing the frictional forces. It provides the cornea with oxygen from the surrounding air. It protects against eye infections and clears the eyes of dangerous irritants and dirt.

CONJUNCTIVA [56]

The conjunctiva is a thin, translucent mucous membrane that connects the eyeball to the lids. It covers the lids posteriorly, is reflected anteriorly to the sclera, and then merges with the corneal epithelium to form the conjunctival sac, which is open at the palpebral fissure. It typically contains about 7 f.Ll of tear fluid but can accommodate up to 30 f.LI.

The conjunctiva is described in three regions: palpebral, bulbar, and forniceal.

1). THE PALPEBRAL CONJUNCTIVA:

This may be subdivided into the Marginal, Tarsal and Orbital zones. –

- The marginal conjunctiva is a transition zone between skin and the conjunctiva proper.
- The tarsal conjunctiva is thin, adherent and very vascular.
- The orbital conjunctiva of the upper lid is between the tarsal upper border and fornix.

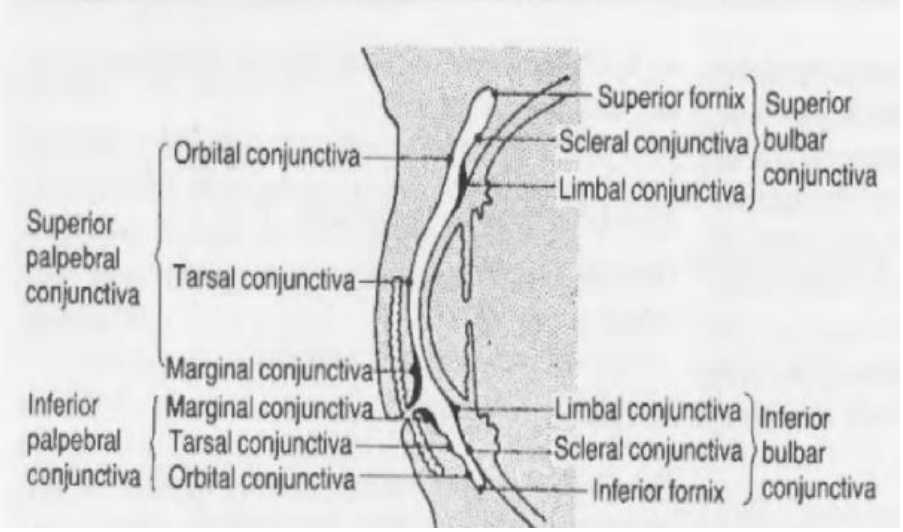


Figure 14. (a) Diagrammatic representation of the conjunctival sac in vertical section of the closed eye,

2). THE CONJUNCTIVAL FORNIX:

This is a continuous annular cul-de-sac. It is divided into superior, inferior, lateral and medial regions.

3). BULBAR CONJUNCTIVA:

Thin, and translucent that underlying sclera appears white, the bulbar conjunctiva is tied to adjacent structures by areolar tissue, and is thus mobile enough to allow ocular movement.

HISTOLOGY OF CONJUNCTIVA- [56]

Histology of Conjunctiva varies from region to region, and like other mucous membranes, conjunctiva has an epithelium, sub mucosal lamina propria. The palpebral margin is covered by keratinised stratified epithelium. At mucocutaneous junction, the epithelium changes in to non- keratinised squamous cells in about five strata, all nucleated.

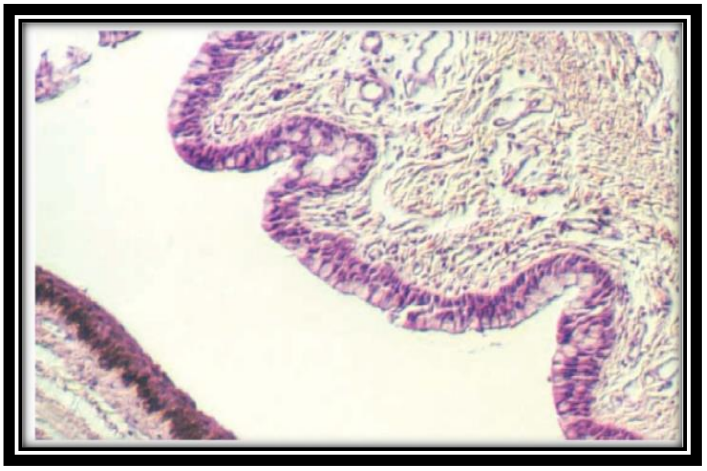


Figure 15: Epithelium of conjunctiva with goblet cells.

The intermediate layers of polyhedral cells, with the most superficial being flat but indented, are seen in the basal epithelium, which has papillae and cylindrical cells similar to those found in the epidermis. Goblet cells, absent at the mucocutaneous junction, begin to appear and increases in number beyond the subtarsal fold (Kessing, S.V. (1968))[40]

The inferior tarsal conjunctiva is composed of three to four layers, with cubical basal cells and layers of polygonal cuneiform and conical cells between them. The superior tarsal conjunctiva has two layers with a deeper layer of cylindrical cells and superficial layer of cylindrical cells. Toward the fornix, there are three layers. The cells on the outermost layer of the skin have a glycocalyx that will stain positively for glycoprotein.

From fornix to limbus, epithelium becomes less glandular, losing its goblet cells, and more epidermal in type but it is never keratinsed. At the limbus, the epithelium is stratified, and papillae form, forming a characteristic sinuous pattern.

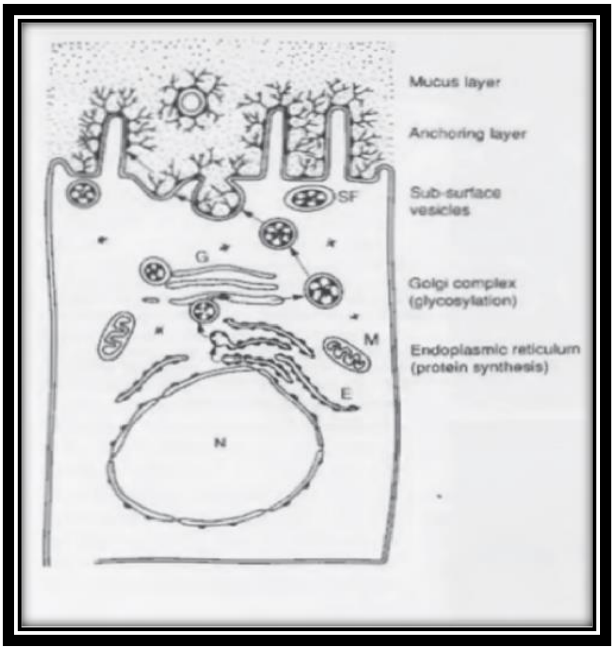


Figure 16: Glycocalyx and mucin layer.

Goblet cells:

These can be seen alone or in conjunction with epithelial crypts across the conjunctiva, particularly in the plica semilunaris. According to Kessing in 1966 and 1968, they are absent at the palpebral mucocutaneous junction and the limbus, and are least dense nasally and in the upper temporal fornix. Goblet cells most likely develop from the epithelium's basal layer and have a propensity to stay attached to the basement membrane.The cells are round or oval in shape, 10-20 m broad, and have flat basal nuclei. As they go closer to the surface, where they form stomas and release their mucin, the cells get bigger and more oval.

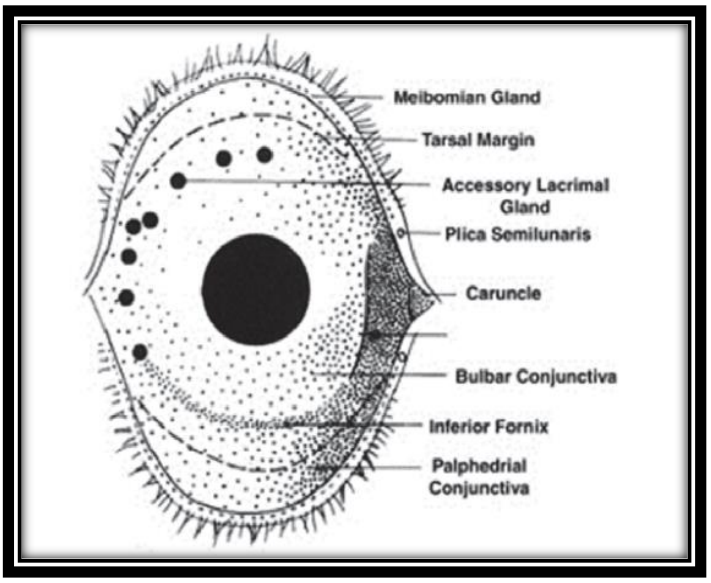


Figure-17: Distribution of goblet cells in conjunctiva.

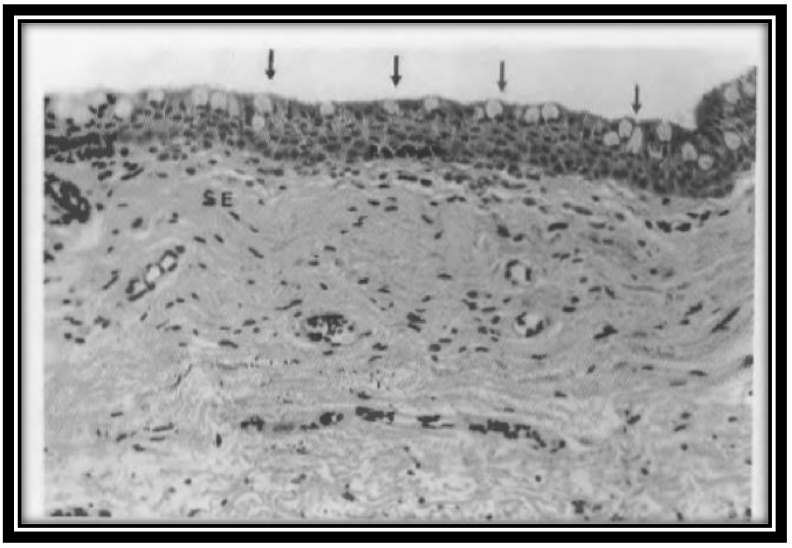


Figure 18. light micrograph of human bulbar epithelium showing mature goblet cells (arrowed) at the epithelial surface

Goblet cells have abundant secretory granules each measuring 0.4- 10 nm in diameter. They contains largest granules closest to the apical membrane. According to Pfister in 1975 and Greiner et al in 1981, when the apical aspect of the goblet cell reaches the epithelial surface, it

presents a number of surface microvilli. These microvilli are gradually lost as the cell distends prior to secretion of mucin.

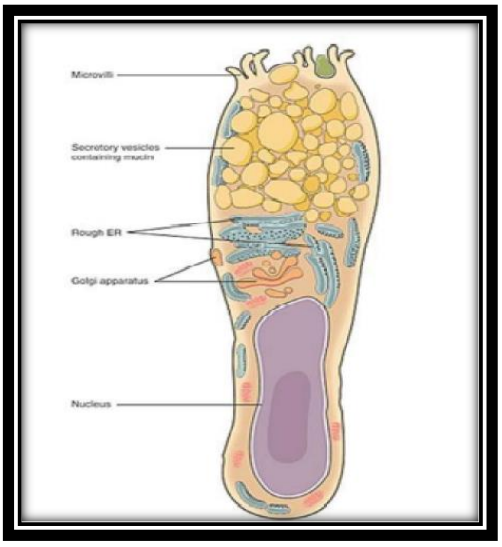


Figure 19 : Structure of goblet cell

THE ACCESSORY LACRIMAL GLANDS[56]

Two groups of accessory lacrimal glands are associated with the conjunctiva.

Glands of Krause:

According to Krause 1867, these glands lie mainly in the deep subconjunctival tissue of the upper fornix (about 42), between the palpebral part of the lacrimal gland and the tarsal plate, and also in the lower fornix (6-8). They form a single duct that discharges into the fornix after joining their ductules.

Glands of Wolfring:

The glands of Wolfring are larger than those of Krause. There are two to five above the superior tarsus or within its upper border near the mid point and two within the lower edge of the inferior tarsus.

Henle's 'glands' are merely folds of mucous membrane between the fornices and tarsal plates.

The glands of Manz, present at the limbus in some ungulates, are not found in humans.

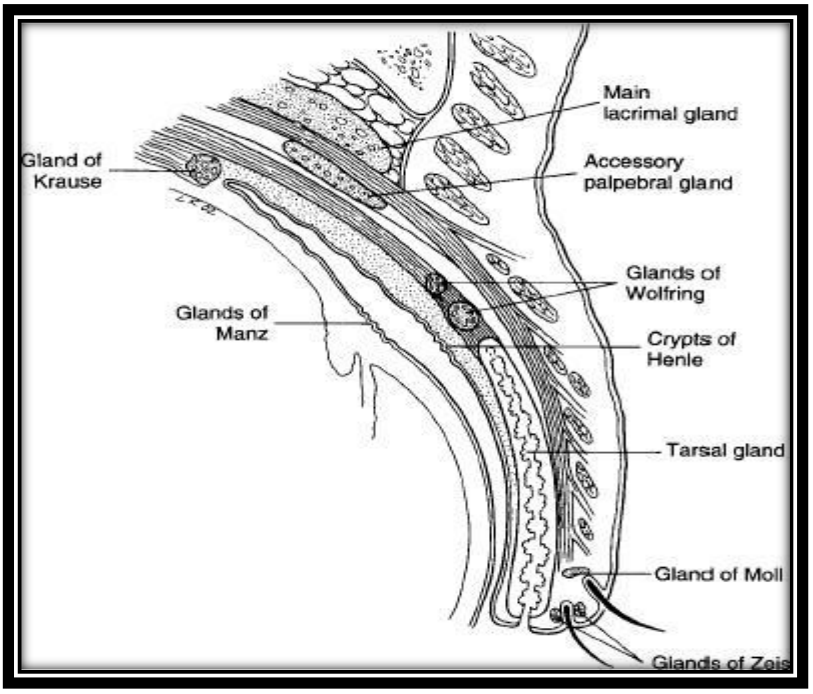


Figure 20. conjunctival glands

DRY EYE DISEASE:

DEFINITION: "A multifactorial condition of the tears and ocular surface known as dry eye causes symptoms such as pain, blurred vision, and tear film instability as well as the possibility of ocular surface injury".

- It is accompanied with ocular surface irritation and an increase in the osmolarity of the tear film.
- Dry eye is a disturbance of the *Lacrimal Functional Unit* (LFU).[57]

The LFU serves to preserve, the transparency of the cornea, and the tear-film integrity.[58,59]The role that sensory impulses play in the system is an essential component. These ocular surface-derived impulses keep the tear flow in resting state.It is currently believed that awake tear flow is a reflex reaction to afferent

impulses, specifically those originating from the ocular surface. It is believed that sensory information from the nasal mucosa also plays a role.[60] Any injury or disease of the-LFU could make the tear film fragile, which could result in a condition on the ocular surface known as dry eye.

CLASSIFICATION OF DRY EYE [61]

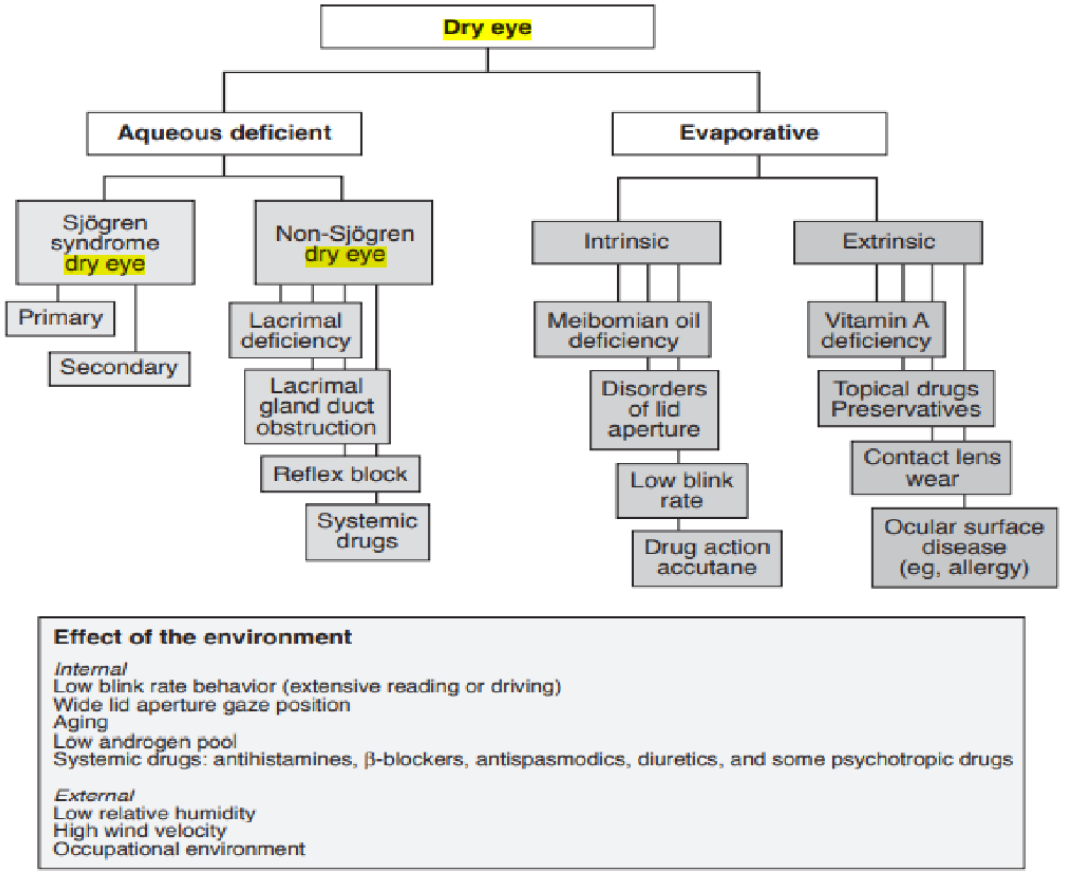


Figure 21. Classification of dry eye diseases

Aqueous Tear Deficient Dry Eye (Tear Deficient Dry Eye/ Lacrimal Tear Deficiency)

- Aqueous-deficient dry eye implies a failure of lacrimal tear secretion.
- In this form of dry eye, lacrimal acinar destruction or dysfunction occurs, results in reduced lacrimal tear secretion and volume of tears [63,63] resulting

in tear hyperosmolarity, due to evaporation of water from a reduced aqueous tear pool.

Mechanism:

The production of inflammatory-cytokines like IL-1, and tumour necrosis factor as well as MMPs is triggered by the hyperosmolarity of the tear-film, which causes the ocular- surface epithelial cells to become hyperosmolar. These events involve MAP kinases and NFkB signalling pathways(MMP-9)**.**[64,65,66]

A) <u>AQUEOUS DEFICIENT :</u> It has 2 major sub classes:

- Sjogren Syndrome Dry Eye (SSDE)
- Non Sjogren Syndrome Dry Eye (NSSDE).

1) <u>SJOGREN SYNDROME DRY EYE</u>

- Sjogren syndrome is an exocrinopathy affecting the lacrimal and the salivary glands by a targeted autoimmune process. (Other organs may also be affected)
- There is infiltration of activated T-cells in the lacrimal and salivary glands which causes acinar and ductular cell death along with hyposecretion of the tears and saliva.

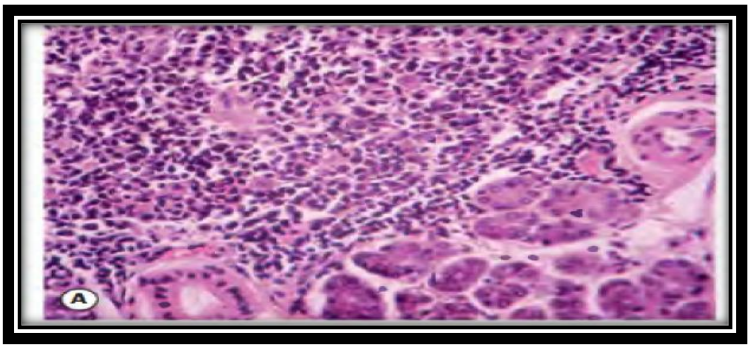


Figure 22: Sjögren syndrome. (A) Histology of the lacrimal gland showing lymphocytic infiltration

Due to an inflammatory activation within the glands, autoantigens (such as fodrin, Ro, and La) are produced on the surface of epithelial cells, and tissue-specific CD4 and CD8 T lymphocytes are also retained.[68]

There are two forms of Sjogren Syndrome (SS):

1. **Primary SS:** consists of the occurrence of an Aqueous Deficient Dry Eye in combination with symptoms of dry mouth, due to the presence of autoantibodies.

- This is characterized by reduced salivary secretion. [72,73]

2. **Secondary SS**: consists of all the features of primary SS in addition to the features of an overt autoimmune connective disease, such as Rheumatoid arthritis (most common), Polyarteritis Nodosa (PAN), Systemic Lupus erythematosus (SLE), Wegener's granulomatosis.

2) Non Sjogren Syndrome Dry Eye

- It is also a form of ADDE due to lacrimal dysfunction, but in this case the systemic autoimmune features characteristics of SSDE have been excluded.

It includes the following:

a) LACRIMAL DEFICIENCY:

PRIMARY LACRIMAL GLAND DISORDERS:

- ***Age related***: Lacrimal gland ductal and acinar pathology occuring due to low grade dacroadenitis, conjunctivitis or any systemic infection.
- ***Congenital Alacrimia***: rare in occurrence and has been associated with syndromes.
- ***Familial Dysautonomia***: (Riley Day syndrome) multisystem disorder associated with decreased emotional and reflex tearing.

SECONDARY LACRIMAL GLAND DISORDERS

- Lacrimal gland infiltration in sarcoidosis, lymphoma, AIDS, Graft Versus Host Disease

b) OBSTRUCTION OF LACRIMAL GLAND DUCTS

- Any cicatrisation occurring due to trachoma, pemphigoid, erythema multiforme, chemical or thermal burns.

c) REFLEX HYPOSECRETION:

- **Sensory reflex block**: A reduction in sensory drive leads to reduced blinking along with hyposecretion
  a. Contact lens wear: hard and extended wear lenses
  b. LASIK: due to denervation
  c. Diabetes: sensory or autonomic neuropathy, due to microvascular changes occuring in the lacrimal gland
  d. Neurotrophic keratitis
- **Reflex motor block**: Central damage to seventh nerve including nervus intermedius with loss of secretomotor function and lagophthalmos.

B) **Evaporative Dry Eye (EDE)**

- When there is excessive water loss from the exposed ocular-surface, instead of normal lacrimal-gland function, it results in evaporative dry eye.

Its causes have been described as:

- Intrinsic: due to intrinsic disease affecting lid structures or dynamics.
- Extrinsic: ocular surface disease occurs due to extrinsic exposure.

1) <u>INTRINSIC CAUSES:</u>

a) Meibomian Gland Dysfunction:

MGD is the most frequent cause for evaporative DED. Simple or cicatricial MGD might be primary or secondary,[74,75] There are various methods to grade the degree of MGD,[76] and measure the degree of gland dropout (meibography)[77,78] and the amount of oil in the lid margin reservoir (meibometry)[79,80]

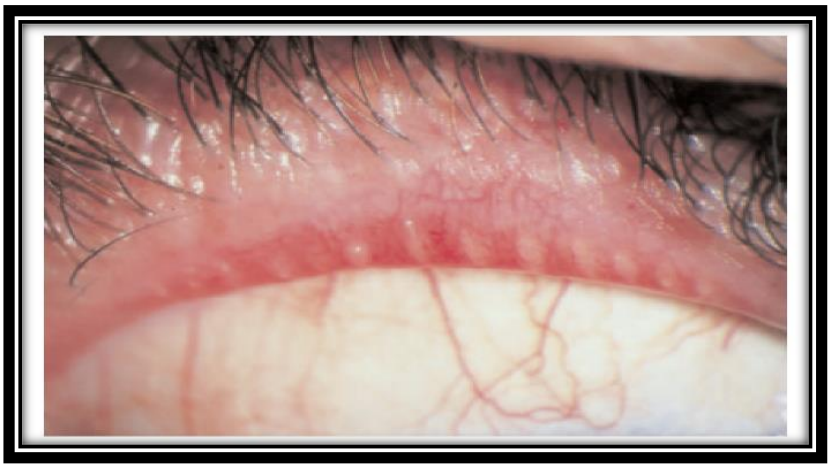


Figure 23: Meibomian gland dysfunction.

a) Disorders of Lid Aperture and Lid/Globe congruity:

- Due to excess evaporation from the ocular-surface that is visible in severe proptosis, craniostenosis, and myopia.[81]

c)Low Blink Rate:

- A reduced blink rate lengthens the period during which the ocular surface is exposed to evaporation before the next blink.[82]

2)<u>EXTRINSIC CAUSES:</u>

- Ocular Surface Disorders: May be caused by Vitamin A deficiency and the effects

of chronically applied topical anesthetics and preservatives.

- Contact Lens Wear: The primary reasons for Contact Lens intolerance are discomfort and dryness.[83,84]

- Ocular Surface Disease and allergic conjunctivitis: [85,86]

Tear Hyperosmolarity:

Hyperosmolarity is the primary factor that causes inflammation and damage to the ocular-surface.[87]

Tear Film Instability:

If the TFBUT is less than the blink interval, then it is implied that tear film breakup in that individual is occurring normally in the waking state.

- **Ocular Protection Index**: is the ratio of Tear film break up time divided by blink interval. A value of less than 1 indicates that the tear film breakup occurs in the waking, open-eye condition.

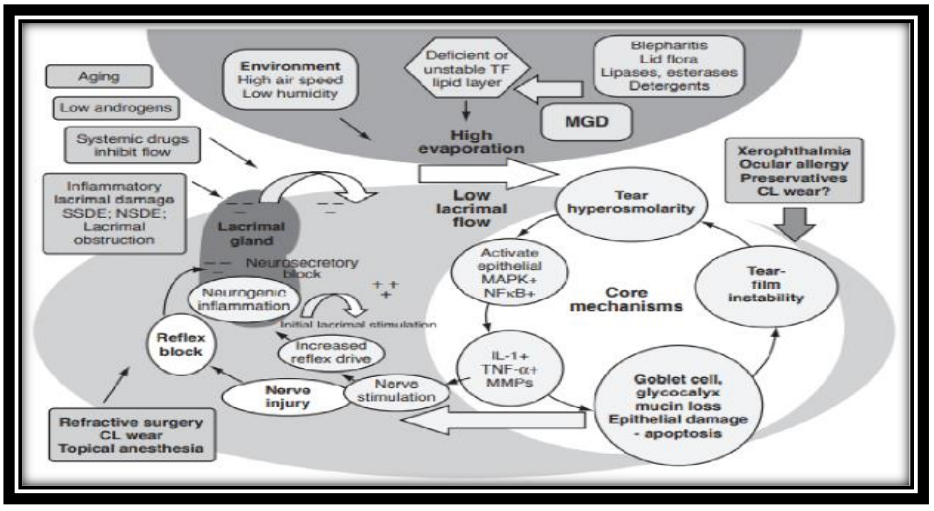


Figure 24: The mechanisms of dry eye.

CLINICAL FEATURES

Symptoms

Dryness, gritty feeling, and burning are the most common ocular symptoms, and these symptoms often get worse during the day. Crust on the eyelids, redness, and stringy discharge are other typical symptoms.The symptoms of KCS are frequently aggravated by prolonged reading or use of a video display device, which reduces blinking, or by exposure to settings that induce more tears to evaporate (such as air conditioning or wind).

Signs

Posterior (seborrhoeic) blepharitis with meibomian gland dysfunction is often present.

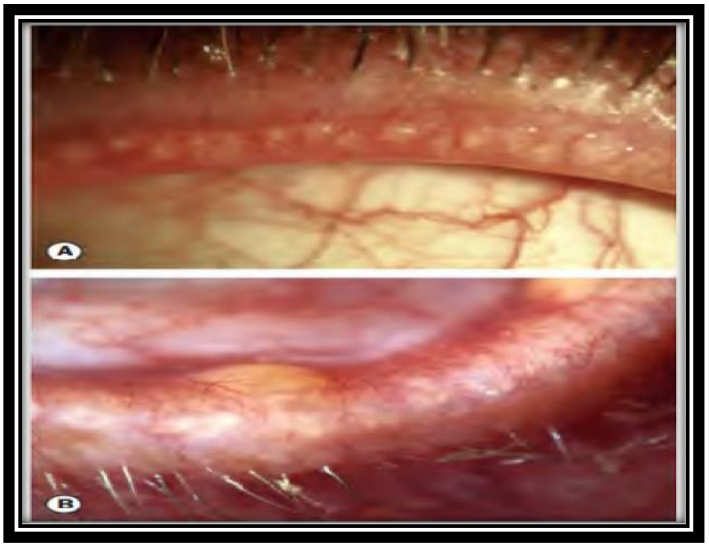


Figure 25: Posterior blepharitis in dry eye. (A) Oil globules at meibomian gland orifices; (B) inflamed meibomian gland

Conjunctiva: Redness, staining with fluorescein, lissamine green and rose Bengal, Keratinization, conjunctivochalasis is a common response to, and exacerbating factor for, the chronic irritation of dry eye, such that a self-sustaining cycle is maintained.

Tear film

In a healthy eye, the mucin layer becomes lipid-contaminated as the tear film degrades but is wiped away.The lipid-contaminated mucin that is present in dry eyes builds up in the tear film as particles and debris that migrate with each blink.The marginal tear meniscus (strip), which measures the amount of aqueous in the tear film, is a rough estimate. The meniscus is 0.2–0.4 mm thick in a healthy eye, but it gets thin or even disappears in dry eye.

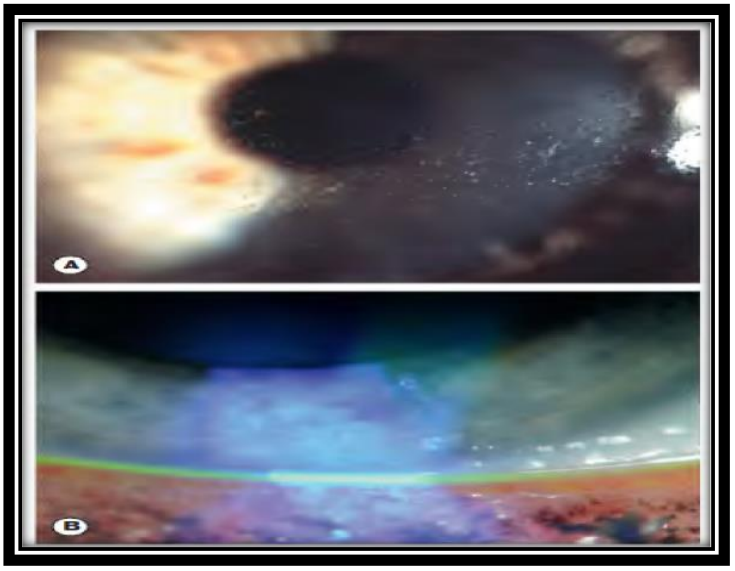
- 

Figure 26: Tear film abnormalities in dry eye. (A) Mucous debris; (B) thin marginal tear meniscus

Cornea

Punctate epithelial erosions that stain well with fluorescein. Filaments stain well with rose Bengal but less so with fluorescein. Mucous plaques with similar constituents that may occur in severe dry eye.

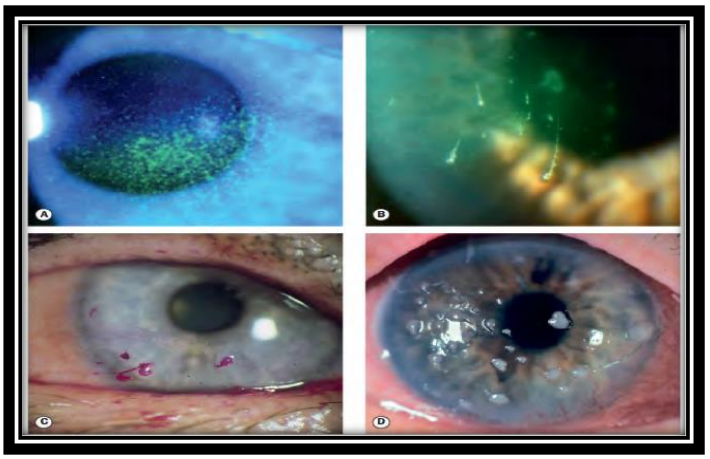


Figure 27: Corneal signs in dry eye. (A) Punctate erosions stained with fluorescein; (B) corneal filaments; (C) mild (rose Bengal stain) and (D) severe mucous plaque formation

INVESTIGATION

The aim of investigation is to confirm and quantify a clinical diagnosis of dry eye. The reliability of tests improves as the severity of dry eye increases. The tests measure the following parameters:

1). TEAR MENISCUS HEIGHT

- The tear film meniscus quantifies the tear film's volume in the least invasive way possible. It will be measured using slit light biomicroscopy.
- The lower meniscus height will then be determined by reading it off the scale on the reticule of the slit lamp after a normal blinking period. A measurement that is less than 0.35 mm will be considered abnormal.

2). SCHIRMER TEST I

The Schirmer test is a frequently used, low-cost, and straightforward clinical procedure for measuring tear production. The Schirmer's test was initially introduced by Otto Schirmer in 1903. It is still the approach that clinicians employ the most frequently to gauge aqueous tear production, according to Kashkouli et al in 2010. Halberg and Behrens initially introduced the standardised Schirmer test

strips in 1961. De Roetth converted to Whatman standard No. 41 filter paper in 1953. For this test, a Whatman number 41 strip that is 5 mm wide and 35 mm long will be used. The basal schirmer's test or the ST without anaesthesia are both highly standardised tests that are used to quantify the basal tear secretion brought on by the conjunctival-lacrimal trigeminal reflex.[75,76]

Figure 28. Whatman 41 SCHIRMER'S STRIP

In a research conducted in 2010, Kashkouli et al. substituted a one-minute test period for the standard Schirmer test's five-minute duration. He discovered a strong correlation between two tests and came to the conclusion that this approach was effective since it was quicker and more pleasant for the patient. [77] In a related study done in 2010, Karampatakis et al. used tests that lasted two minutes as opposed to five. All study participants favoured the shorter time limit and were more at ease with the two-minute process, they concluded after finding a similar association between the two tests. 78

Numerous studies have looked at where the Schirmer strip should be placed on the lid margin, but it has been demonstrated that there are no discernible differences between positioning the paper at the medial or lateral site of the lower lid edge (Loran et al, 1987).[79]

. According to a study by Kashkouli et al. (2010), since the closed eye state cancels out the effects of external factors like temperature, evaporation, and humidity, it helps to maintain

more uniform and consistent test settings.[77] In 2010, Karampatakis et al also conducted study by reducing the test time to two minutes instead of five minutes and he also found a similar correlation between two tests and he concluded that all the study participants preferred the shorter duration and were more comfortable with the 2-minute procedure.[78] Numerous studies have looked at where the Schirmer strip should be placed on the lid margin, but later it was demonstrated that there are no differences between positioning the paper at the medial & lateral site of the lower lid edge (Loran et al, 1987)".[79]

PROCEDURE

- This test will be performed without topical anaesthesia under natural lighting.
- A standardized filter paper will be used.
- About 5mm of the Schirmer strip was bent and placed in the lower fornix at the junction of middle and lateral thirds of the lower fornix, the eyes were left closed for 5 min and the distance moistened will be measured on the scale on the filter paper itself.
- A reading of <10mm will be considered abnormal.

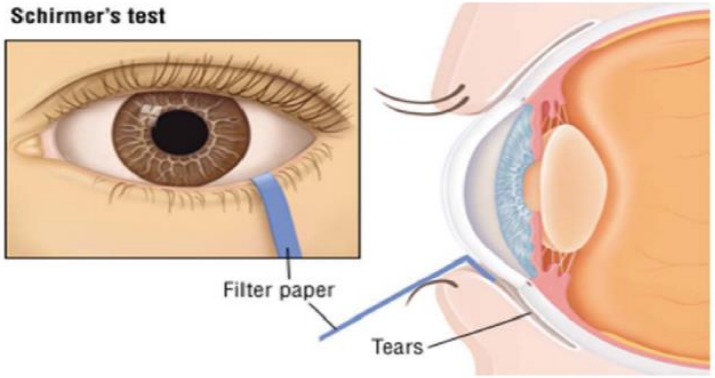


Figure- 29: Procedure of schirmers test.

3). SCHIRMER TEST II

- This test will be performed with topical anaesthesia, the remaining procedure is similar to Schirmer test I.
- Schirmer II test is used to measure reflex secretion of tears.
- The value of < 6mm will be considered abnormal.

4). TEAR BREAKUP TIME[73,88]

Tear film break up was first described in 1969 by Norn later popularized by Lemp and Hamill in 1973. It is a useful technique for figuring out how stable the preocular tear film is. The patient was told to blink three times and then look straight ahead without blinking after inserting a fluorescein-impregnated strip and moistening it with non-preserved saline.With a cobalt blue filter, wide beam illumination, and a slit lamp biomicroscope, the tear film will be examined. The amount of time (TBUT) that passed between the last blink and the first dry spot on the cornea was recorded. A value of less than 10 seconds will be deemed abnormal. It is reduced in patients with mucin deficiency and who have severe aqueous deficiency.

Figure- 30: Fluorescein 1.0 mg strips

- 1973, Holly made the discovery of TBUT; with each blink, the tear film gradually becomes thinner due to evaporation. Some lipid molecules start to be drawn to and travel down to the mucin layer when the tear film thins to a certain threshold thickness. When the mucin layer of the endothelium is sufficiently polluted with lipid from thetop,

the tear film separates and a dry area is produced. These dry spots usually appear 15 to 30 seconds after a blink in irregular places on the corneal surface. Blinking can repair this and restore the aqueous layer, thus normally the blink interval is shorter than the break up time.[89]

A study was done in 1983 in Aligarh to know the BUT in normal Indian subjects, as previously no study was done on BUT in this part of the world. It was reported that BUT was less than 15 seconds when compared to westerners in whom it was twenty to thirty seconds normally. The reduced rate was attributed to tropical climate conditions.[90]

- 2005 saw the completion of another study in Canada examining the dynamics of tear film breakage in dry eyes and healthy individuals, as well as its influence on dry eye symptoms. This study unequivocally demonstrated that dry eye individuals experience a more quick and widespread TBUT than controls.[91]

5). OCULAR SURFACE DISEASE INDEX (OSDI)

- Patients were also assessed with the OSDI questionnaire on the basis of the severity of their subjective symptoms.
- The OSDI was developed to provide a rapid assessment of the severity of symptoms of OSD and their impact on vision-related function.
- The twelve items of the OSDI questionnaire are graded on a scale of 0-4:
- 0 = presence of symptoms none of the time;

1= some of the time

2= half of the time

3= most of the time

4= all the time.

- Total OSDI scores were calculated for each patient using the formula:

- OSDI= (sum of scores for all questions answered) x 25/ (total number of questions answered). Thus, the OSDI was scored on a scale of 0 to 100.

0-12 = Normal

13 – 22 =Mild dry eye

23- 32 = Moderate dry eye

>33 = Severe dry eye

- A score of 15 has moderate sensitivity and specificity, 60% and 83%, respectively, for the diagnosis of dry eye disease.[92]
- The following 12 questions should be asked, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK:

Questions	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**
Eyes that are sensitive to light?	4	3	2	1	0
Eyes that feel gritty?	4	3	2	1	0
Painful or sore eyes?	4	3	2	1	0
Blurred vision?	4	3	2	1	0
Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 =

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK:

Questions	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	
Reading?	4	3	2	1	0	NA
Driving at night?	4	3	2	1	0	NA
Working with computer?	4	3	2	1	0	NA
Watching TV?	4	3	2	1	0	NA

Subtotal score for answers 6 to 9 =

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK:

Questions	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	
Windy conditions?	4	3	2	1	0	NA
Places or areas with low humidity (very dry)?	4	3	2	1	0	NA
Areas that are air conditioned?	4	3	2	1	0	NA

- OSDI Score is assessed on a scale of 0 to 100, with higher scores representing greater disability.

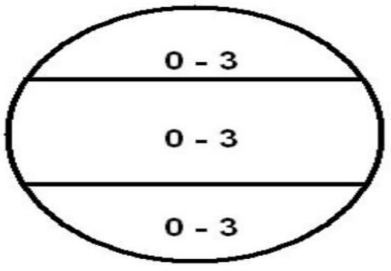
- The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease.
- The OSDI is a valid and reliable instrument for measuring dry eye disease.

6). CORNEAL FLUORESCEIN STAINING

- The use of dyes can help assess the superficial ocular surface to detect damage that can be present in dry eye disease.
- These dyes include fluorescein, lissamine green and rose bengal. These evaluations are cheap and easy to perform clinically.

PROCEDURE

- A fluorescein paper will be moistened with normal saline and applied at the lower fornix and patients will be asked to close and open eyes for the proper distribution of the dye around the cornea.
- Corneal staining pattern is graded for the superior, central and inferior areas, in a score ranging from 0 (no staining) to 3 (continuous epithelial defect) and registered in a diagram. The total score is the sum of the three areas, with a maximum score of 9.
- Values of a score above three were considered abnormal.



Fluorescein staining pattern for the cornea: division of superior, central, and inferior areas. Each area ranges from 0 (no staining) to 3 (continuous epithelial defect), with a maximum score of 9.

7). CONJUNCTIVAL IMPRESSION CYTOLOGY

- Impression cytology refers to the application of a cellulose acetate filter to the ocular surface to remove the superficial layers of the ocular surface epithelium.
- These cells can then be subjected to histological, immunohistological, or molecular analysis.
- Egbert et al first described this minimally invasive method of studying conjunctival goblet cells in 1977.[93]
- It is non-invasive, simple to use, and produces accurate results regarding the area tested while causing the patient the least amount of discomfort. This makes it an important tool for comprehending ocular surface diseases.

HISTORY:

- Egbert et al used Millipore filters to collect conjunctival specimens, which were then air dried and stained with periodic acid Schiff (PAS) and haematoxylin.[93]
- Tseng modified the method of collection of specimens by staining the specimen with combination of PAS and Papanicolaou stains.[94]
- Maskin and bode have described a technique with which conjunctival epithelial cells acquired by impression cytology can be studied by electron microscopy.[95]
- Pure nitrocellulose membranes and Biopore membrane devices have been used to enable immunocytochemical staining.[96,97]
- Morphologically Egbert first used this method to determine the density of goblet cells in different areas of the conjunctiva.[93]

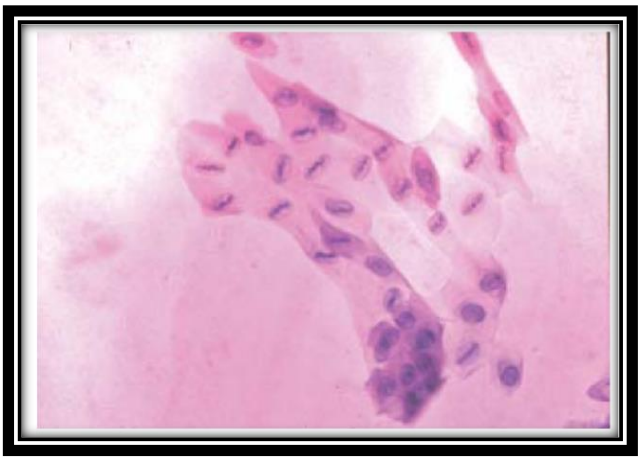


Figure- 31. Impression cytology of the conjunctival surface showing snake-like chromatin in keratoconjunctivits sicca

SAMPLE COLLECTION-

- Most authors use surfactant free filter paper of a pore size between 0.22 mm and 0.44 mm .[99]
- Tseng's modified method of specimen collection uses cellulose acetate filter paper from Millipore, which is trimmed into a 5 mm strip with one square end and one tapering end.
- The asymmetrical shape with a pointed tip facilitates grabbing and transferring the paper to the desired area with blunt smooth edged forceps.[94]

STEPS :

- Cellulose acetate filter paper, precut into 5 X 5-mm pieces with a pointed tip on one corner.
- Blunt, smooth-ended forceps grasped the point and applied the paper to the bulbar conjunctiva near the limbus.

- A smooth glass rod held in the other hand, used to gently press the paper onto the conjunctiva.
- The filter paper is then removed with a peeling motion.
- The filter paper will be on the surface for approximately 3 to 5 seconds.
- The temporal and nasal quadrants of each eye are sampled.
- The tissue is transferred to glass slide and then in to coplin jar containing fixative solution.

Specimen Staining

- Papanicolaou or haematoxylin and PAS stains are the commonly used stains for routine histological staining of impression cytology specimens.
  - The filter paper with the adherent epithelial cells is placed in a fixative solution prepared by mixing 70% ethyl alcohol, 37% formaldehyde, and glacial acetic acid in a 20: l: l volume ratio.
  - Fixation is accomplished in **ten minutes**.
  - The biopsy specimens are then stained with periodic acid- Schiff and modified Papanicolaou's staining All specimens were examined microscopically.
  - An impression cytology usually removes only 1–3 cell layers, it is therefore ideal for studying the surface epithelium rather than the basal epithelium or the basement membrane.

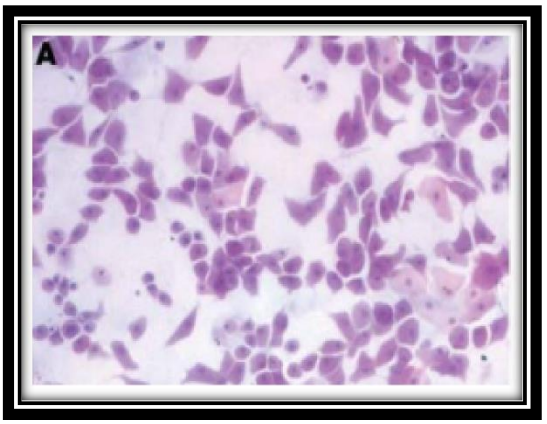


Figure 32. Impression cytology of normal corneal surface showing corneal epithelial cells

- Nelson graded conjunctival impression cytology specimens (grades 0–3) based on the appearance of the epithelial cells and the numbers of goblet cells.[98]

Nelson's Grading

Each sample was graded from 0 to 3 according to Nelson et al, as outlined below.

Grade 0: The epithelial cells are small and round with eosinophilic-staining cytoplasm. The nuclei are large and basophilic, with a nucleus-to-cytoplasm ratio of 1:2. The goblet cells are abundant, plump, and oval and have an intensely PAS-positive cytoplasm.

Grade 1: The epithelial cells are slightly larger and more polygonal and have eosinophilic-staining cytoplasm. The nuclei are smaller, with a nucleus-to-cytoplasm ratio of 1:3. There are fewer goblet cells but they maintain their plump, oval shape with an intensely PAS-positive cytoplasm.

Grade 2: The epithelial cells are larger and polygonal, occasionally multinucleated, with variably staining cytoplasm. The nuclei are small, with a nucleus to- cytoplasm ratio of 1:4 to 1:5. The goblet cells are markedly decreased in number and are smaller and less intensely PAS positive, with poorly defined edges.

Grade 3: The epithelial cells are large and polygonal with basophilic-staining cytoplasm. The nuclei are small, pyknotic and, in many cells, absent. The nucleus-to-cytoplasm ratio is greater than 1:6. Goblet cells are absent.

RECENT ADVANCES

- The impression cytology method, which makes use of pure nitrocellulose membranes and IC staining, was developed to examine the expression of cytokeratin in bulbar conjunctiva.[100]
- The conjunctiva was discovered to exhibit a distinct pattern of cytokeratin expression that included cytokeratins (K4 and K13) typical of non-keratinized, stratified epithelia as well as others (K8 and K19) more typical of a glandular & simple differentiation pattern.[100]
- Conjunctival metaplasia caused by the use of topical antiglaucoma medications has recently been shown using impression cytology. [101,102,103,104]

REVIEW STUDIES:

Shukrullah Noori et al [105] studied a total of 398 eyes of 200 participants and two groups were formed. The first, pseudoexfoliation syndrome (PEXS) group, included 198 eyes of 100 patients, and the second, age-matched control group, included 200 eyes of 100 participants. Tear film abnormalities were compared in the two groups by tear meniscus height (TMH), Schirmer test I, Schirmer test II and tear film break-up time (TBUT). On comparing the two groups using independent t-test, a significant difference was found in Schirmer test I, Schirmer test II, and TBUT between the PEXS group (Schirmer test I: 23.98 ± 10.68 mm, Schirmer test II: 17.11 ± 8.78 mm, and TBUT: 9.778 ± 5.54 s) and the age-matched control group (Schirmer test I: 27.08 ± 9.58 mm, Schirmer test II: 19.98 ± 8.48 mm, and TBUT:

13.495 ± 5.65 s) ($p = 0.003$ [Schirmer test I]; $p = 0.001$ [Schirmer test II]; and $p < 0.001$ [TBUT]). However, an insignificant difference was found in terms of TMH ($p = 0.195$) between the two groups. PEXS affects tear production and leads to unstable tear film.

A Sivaraja Gowthaman et al [2] study was done to assess the prevalence of dry eyes in patients with pseudoexfoliation. This was a descriptive study which involved 150 eyes with pseudoexfoliation syndrome. Tear secretion assessment was done using Schirmer's test I. Then the tear film stability was evaluated using Tear break-up time (TBUT). Ocular surface damage was assessed using Fluorescein staining and Lissamine green staining. Result: Schirmer's test I, 144 eyes out of 150 eyes had Schirmer's test value more than 15 mm (96%). 4 eyes (2.6%) had value between 10-15 mm .2 eyes (1.4%) had value between 5-10 mm. Six eyes with dry eye syndrome were identified by Schirmer's test I. Tear breakup time was decreased in 3 eyes (between 7-9 seconds). Three eyes with dry eye syndrome were identified by the TBUT test. Fluorescein staining was positive in one eye. Lissamine staining was positive in 2 eyes with a score of 2 and 3. In this study of pseudoexfoliation patients, there were 9 eyes(6%) with dry eye syndrome. Early recognition of dry eye syndrome in patients with pseudoexfoliation syndrome can reduce ocular morbidity and prevent a significant compromise in their quality of life.

Ivan Škegro et al [107] determined connection between pseudoexfoliation (PEX) syndrome and symptoms and signs of ocular surface disease. Tear film break-up time test, Schirmer II test and assessment of lid parallel conjunctival folds were performed in 40 PEX syndrome patients and 40 controls. All data was statistically analyzed. Results show statistically significant differences in every component between groups, most prominent in tear film break up time tests. We have concluded that patients with PEX syndrome have higher predisposition of tear function disorders and that both components of dry eye syndrome are present in PEX syndrome.

MATERIALS AND METHODS

4.MATERIALS AND METHODS

SOURCE OF DATA

This cross-sectional study was conducted on a minimum of 45 patients fulfilling the inclusion criteria in the department of Ophthalmology, R. L. Jalappa Hospital and Research centre, Kolar from January 2020 to June 2022, after obtaining ethical clearance from Institutional Ethical Committee of Sri Devaraj Urs Medical College and written informed consent from the subjects.

INCLUSION CRITERIA: All patients of either sex above 40 years of age with pseudo exfoliation

EXCLUSION CRITERIA:

1. Patients on any topical IOP-lowering drugs like Timolol.
2. Patients with lacrimal gland and drainage disorder.
3. History of any ocular surface surgery or ocular trauma.
4. Patients with diabetes mellitus.
5. Thyroid disease patients.
6. Prolonged contact lens wear

METHOD OF COLLECTION OF DATA:

A total of 45 eyes fulfilling the inclusion criteria was included in this cross sectional study. Each patient was assessed by detailed history and clinical examination of both the eyes was done by various methods as follows-

1. Visual acuity assessment by using Snellen chart for distant vision.
2. Near vision by using near vision charts.
3. Slit lamp biomicroscope for evaluation of anterior segment.
4. Posterior segment evaluation done by indirect ophthalmoscopy and +90D biomicroscopy.
5. Assessment of Intraocular pressure by Applanation Tonometer

6. Evaluation of tear film abnormalities by tear meniscus height (TMH), Schirmer test I, Schirmer test II and TBUT (Tear break up time).
7. To assess and grade the ocular surface damage using fluorescein staining and conjunctival impression cytology.
8. Subjective assessment of ocular symptoms using "Ocular Surface Disease Index" questionnaire.

STATISTICAL METHODS USED FOR THIS STUDY

The data that was collected entered in Microsoft Excel 2019 Spreadsheet and analyzed using IBM SPSS 21.0 version. The data on categorical variables was presented as frequency and percentages. Using the chi square test or Fisher exact test, categorical variable distributions were compared. A P value of 0.05 or less was regarded as statistically significant. By using Pearson correlation, the relationship between the severity of dry eye and markers of tear film stability was evaluated. P value of 0.05 or less was regarded as statistically significant. The data was analyzed and interpreted. Charts like bar diagram, pie chart was depicted where ever necessarily.

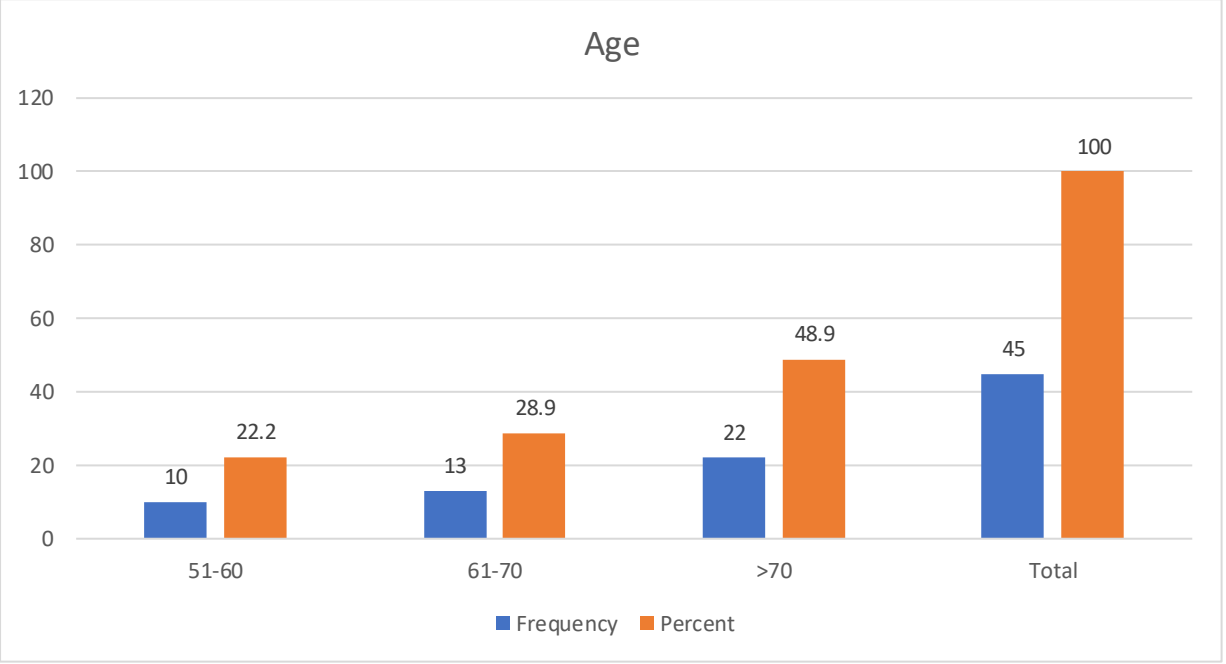
RESULTS

5.RESULTS

Table 3: Frequency distribution of study participants according to age

Age	Frequency	Percent
51-60	10	22.2
61-70	13	28.9
>70	22	48.9
Total	45	100.0

Among study participants, 22(48.9%) were aged >70 years, 13(28.9%) were aged 61-70 years and 10(22.2%) were aged 51-60 years.

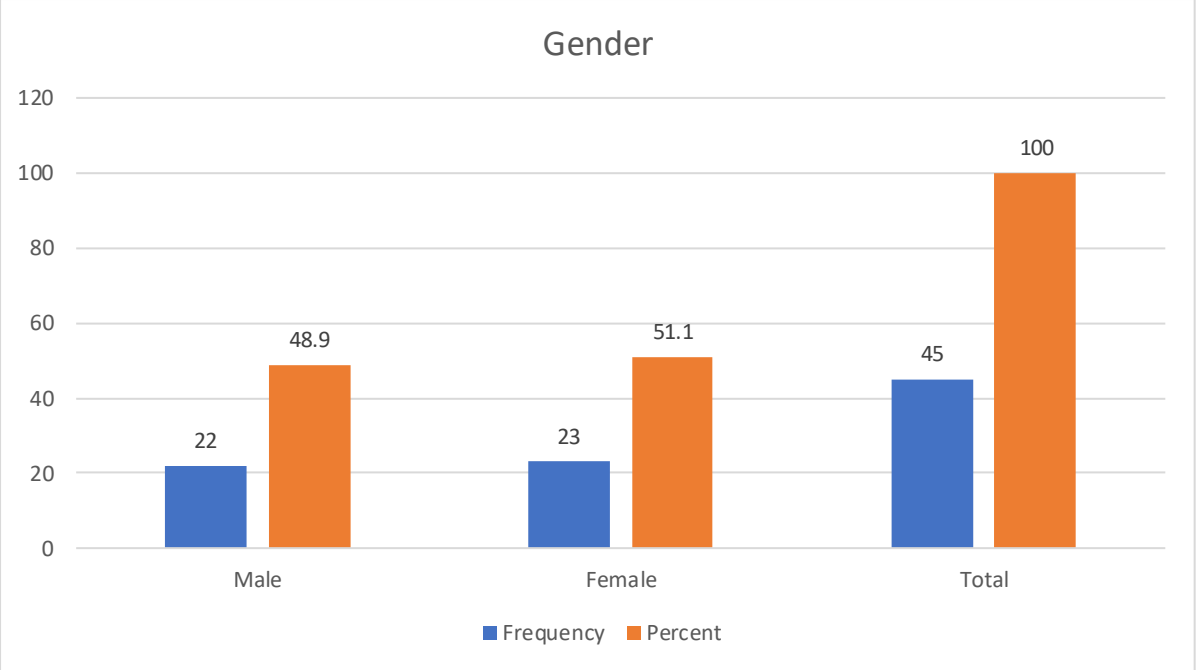


GRAPH 1: Bar diagram of study participants according to age

Table 4: Frequency distribution of study participants according to gender

Gender	Frequency	Percent
Male	22	48.9
Female	23	51.1
Total	45	100.0

Among study participants, males were 22(48.9%) and females were 23(51.1%).

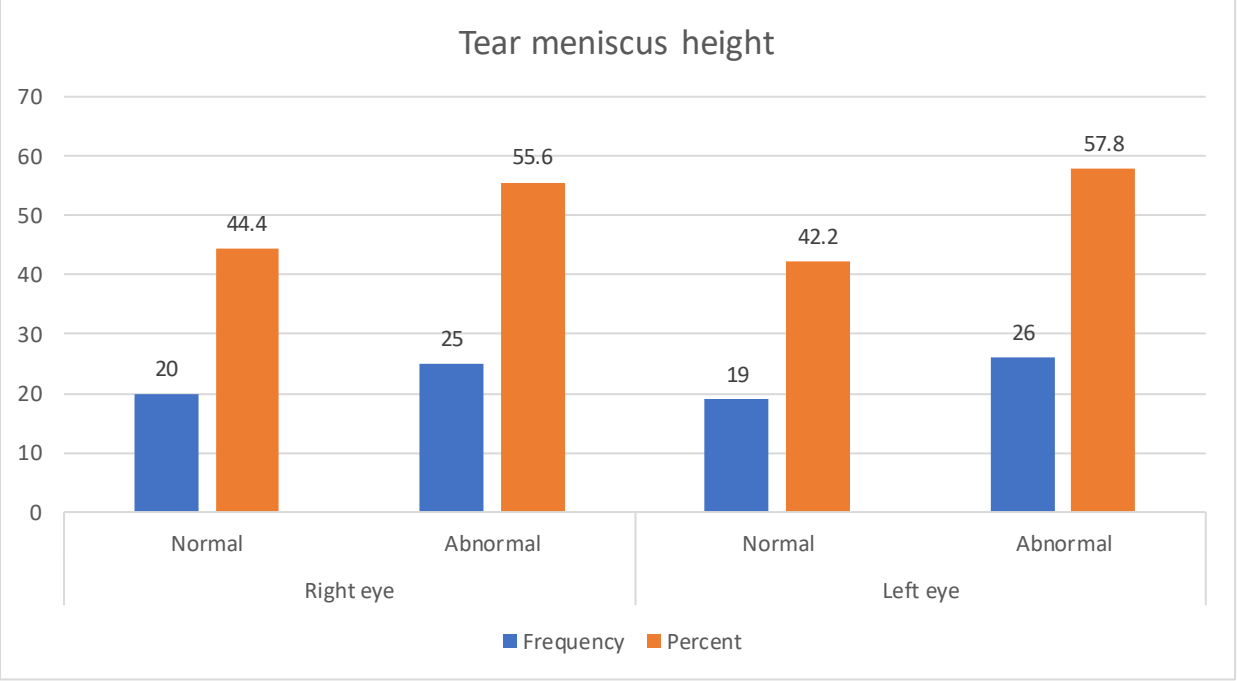


GRAPH 2: Bar diagram of study participants according to Gender

Table 5: Frequency distribution of study participants according to Tear Meniscus height

Tear Meniscus height		Frequency	Percent
Right eye	Normal	20	44.4
	Abnormal	25	55.6
Left eye	Normal	19	42.2
	Abnormal	26	57.8

According to Tear Meniscus height, in Right eye abnormal height was present among 25(55.6%) and Left eye abnormal height was present among 26(57.8%).

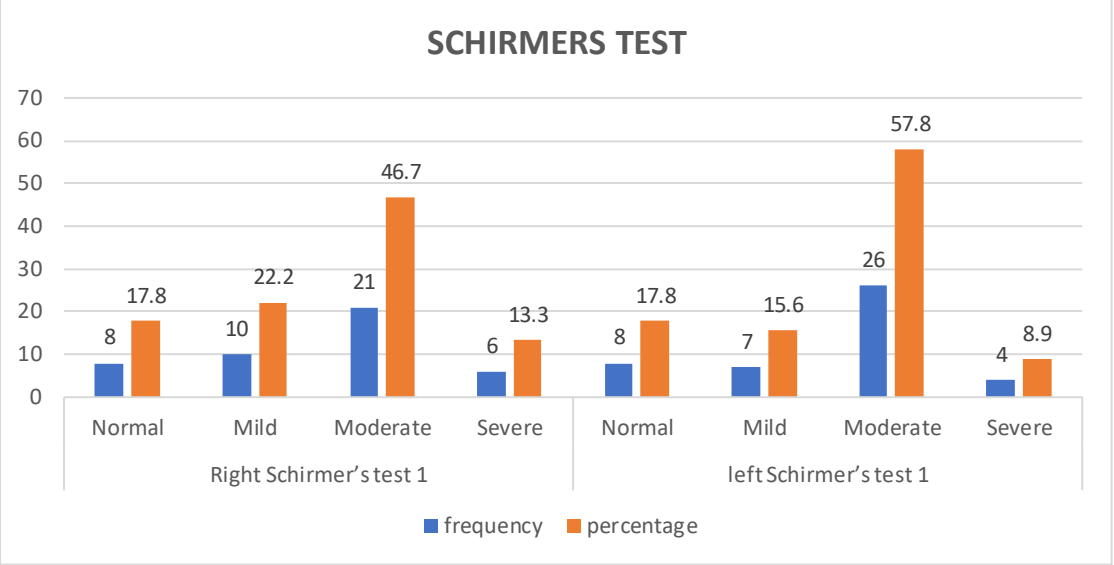


GRAPH 3: Bar diagram of study participants according to Tear meniscus height

Table 6: Descriptive statistics of study participants according to Schirmer's test 1

Schirmer's test 1		**Frequency**	**Percentage**
Right Schirmer's test 1	Normal	8	17.8
	Mild	10	22.2
	Moderate	21	46.7
	Severe	6	13.3
Left Schirmer's test 1	Normal	8	17.8
	Mild	7	15.6
	Moderate	26	57.8
	Severe	4	8.9

According to Schirmer's test 1, among right eye, 21(46.7%) were moderate grade, 10(22.2%) were mild grade, 8(17.8%) were normal grade and 6(13.3%) were severe grade. among left eye, 26(57.8%) were moderate grade, 8(17.8%) were normal grade 7(15.6%) were mild grade and 4(8.9%) were severe grade.

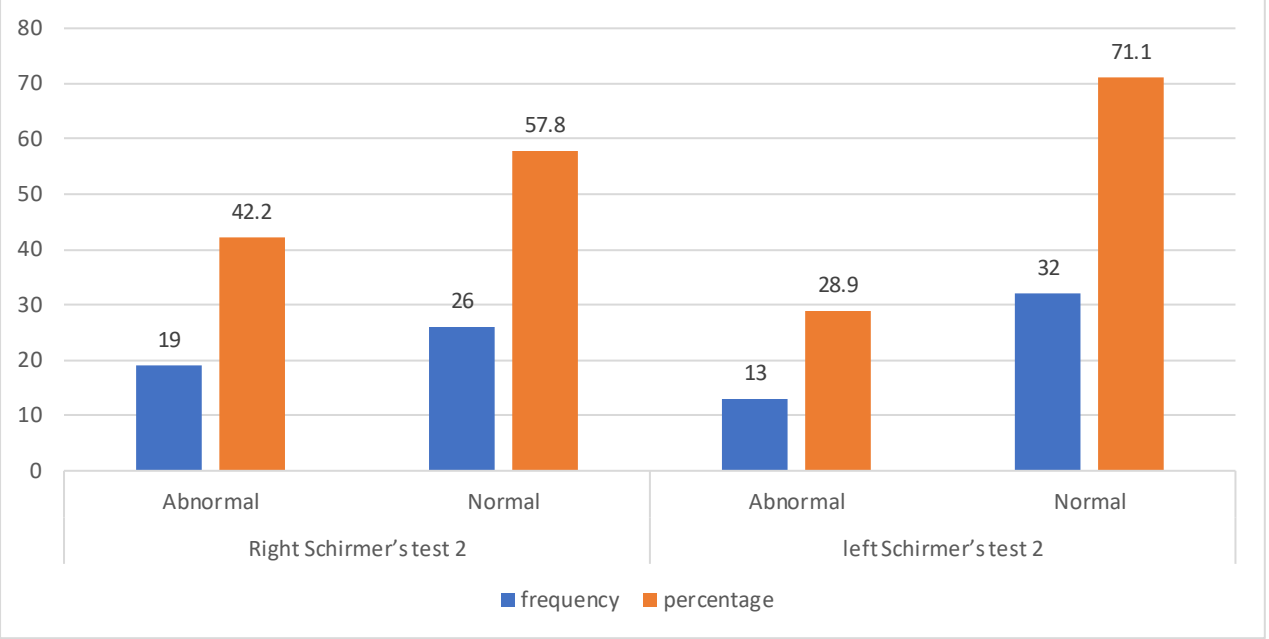


GRAPH 4: Bar diagram of study participants according to Schirmer's test I

Table 7: Frequency distribution of study participants according to Schirmer's test 2

Schirmer's test 2		**Frequency**	**Percentage**
Right Schirmer's test 2	Abnormal	19	42.2
	Normal	26	57.8
Left Schirmer's test 2	Abnormal	13	28.9
	Normal	32	71.1

According to Schirmer's test 2, among right eye abnormal test was 19(42.2%) and among left eye abnormal test was 13(28.9%).

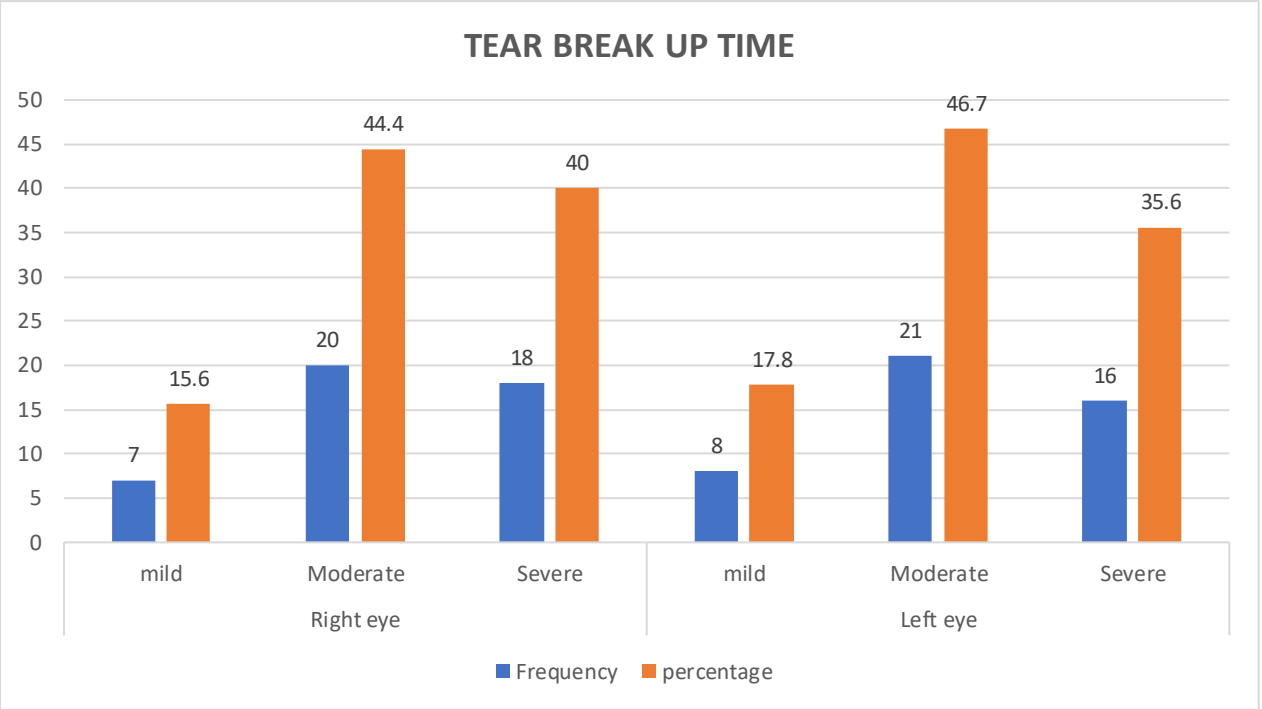


GRAPH 5: Bar diagram of study participants according to Schirmer's test II

Table 8: Frequency distribution of study participants according to Tear Break Up Time (sec)

Tear Break Up Time (sec)		**Frequency**	**Percentage**
Right eye	mild	7	15.6
	Moderate	20	44.4
	Severe	18	40.0
Left eye	mild	8	17.8
	Moderate	21	46.7
	Severe	16	35.6

According to Tear Break Up Time, among right eye, 20(44.4%) were moderate grade, 18(40%) were severe grade and 7(15.6%) were mild grade. among left eye, 21(46.7%) were moderate grade, 16(35.6%) were severe grade and 8(17.8%) were mild grade.

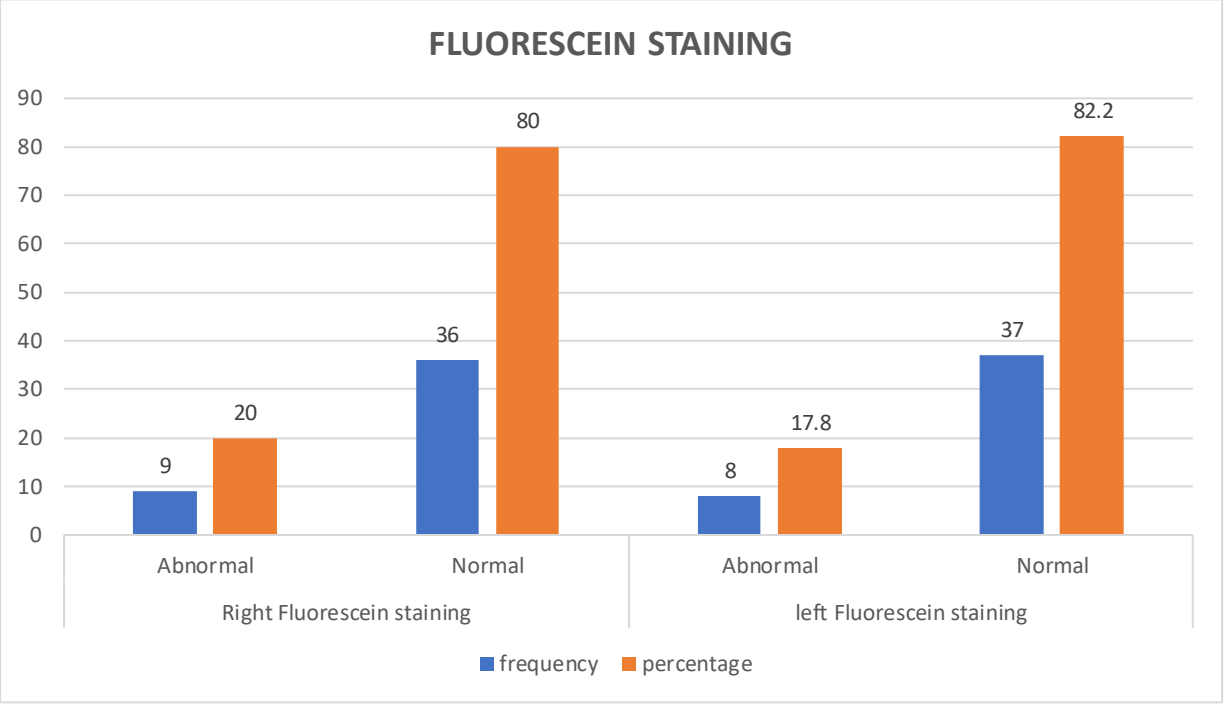


GRAPH 6: Bar diagram of study participants according to Tear break up time

Table 9: Frequency distribution of study participants according to Fluorescein staining

Fluorescein staining		**Frequency**	**Percentage**
Right Fluorescein staining	Abnormal	9	20.0
	Normal	36	80.0
left Fluorescein staining	Abnormal	8	17.8
	Normal	37	82.2

According to Fluorescein staining, among right eye abnormal test was 9(20%) and among left eye abnormal test was 8(17.8%).



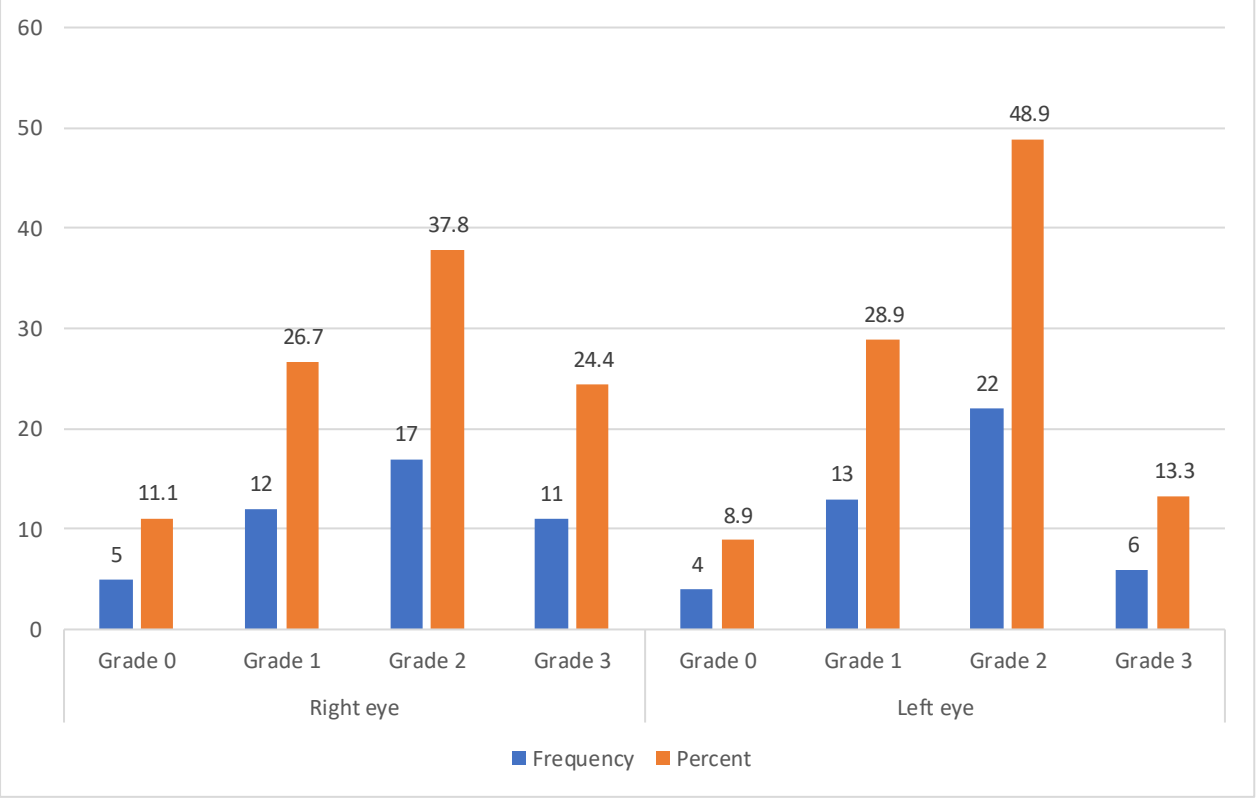
GRAPH 7: Bar diagram of study participants according to Fluorescein staining

Table 10: Frequency distribution of study participants according to Conjunctival impression cytology

Conjunctival impression cytology		**Frequency**	**Percent**
Right eye	Grade 0	5	11.1
	Grade 1	12	26.7
	Grade 2	17	37.8

	Grade 3	11	24.4
Left eye	Grade 0	4	8.9
	Grade 1	13	28.9
	Grade 2	22	48.9
	Grade 3	6	13.3

According to Conjunctival impression cytology, in right eye, 17(37.8%) were grade 2, 12(26.7%) were grade 1, 11(24.4%) were grade 3 and 5(11.1%) were grade 0. in Left eye, 22(48.9%) were grade 2, 13(28.9%) were grade 1, 6(13.3%) were grade 3 and 4(8.9%) were grade 0.

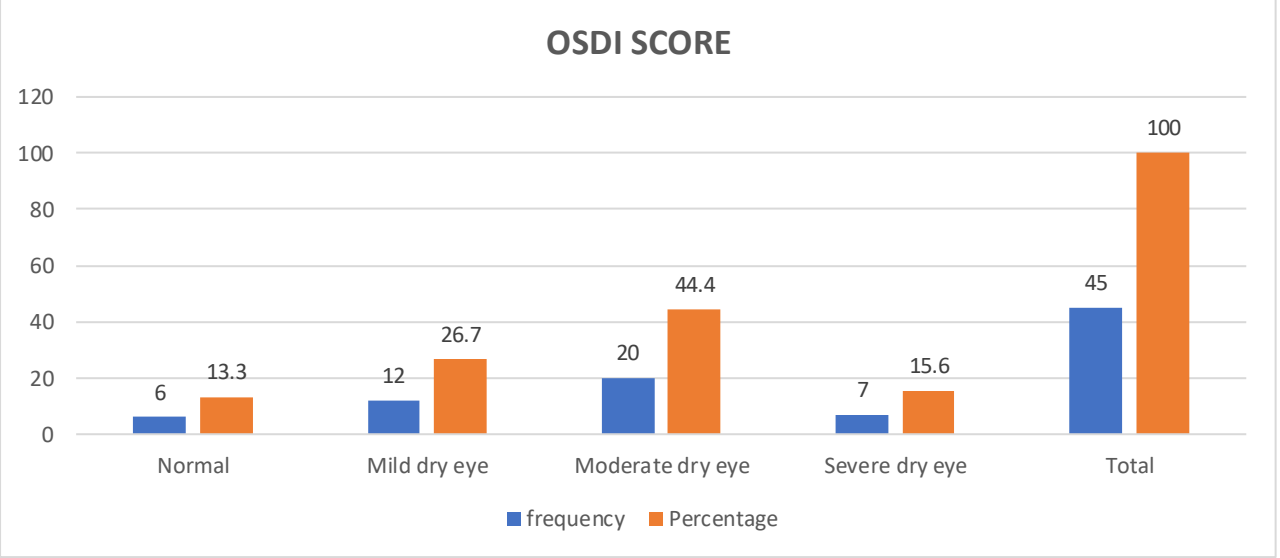


GRAPH 8: Bar diagram of study participants according to Conjunctival impression cytology

Table 11: Descriptive statistics of study participants according to OSDI score

OSD score	frequency	Percentage
Normal	6	13.3
Mild dry eye	12	26.7
Moderate dry eye	20	44.4
Severe dry eye	7	15.6
Total	45	100

Among study participants, moderate dry eye was among 20(44.4%), mild dry eye was among 12(26.7%), severe dry eye was among 7(15.6%) and normal eye was among 6(13.3%).

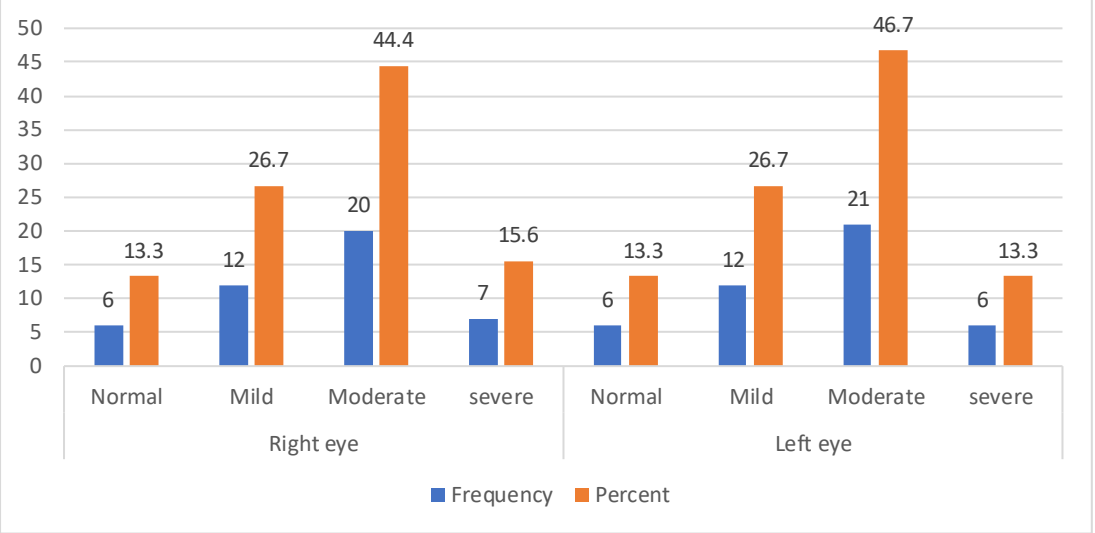


GRAPH 9: Bar diagram of study participants according to OSDI score

Table 12: Frequency distribution of study participants according to Grading of dry eye

Grading of dry eye		**Frequency**	**Percent**
Right eye	Normal	6	13.3
	Mild	12	26.7
	Moderate	20	44.4
	severe	7	15.6
Left eye	Normal	6	13.3
	Mild	12	26.7
	Moderate	21	46.7
	severe	6	13.3

According to Grading of dry eye, in the right eye, 20(44.4%) were moderate grade, 12(26.7%) were mild grade, 7(15.6%) were severe grade and 6(13.3%) were normal grade. in Left eye, 21(46.7%) were moderate grade, 12(26.7%) were mild grade, 6(13.3%) were severe grade and 6(13.3%) were normal grade.



GRAPH 10: Bar diagram of study participants according to Grading of Dry eye

Table 13: Pearson correlation of grading of left Dry eye and various test

Pearson correlation	grading of left Dry eye	
	Correlation coefficient	P value
LT CONJUNCTIVAL IMPRESSION CYTOLOGY	0.959	0.0001
LT FLUORESCEIN STAINING	0.714	0.0001
Left Tear Break Up Time	0.792	0.0001
LT SCHIRMERS 1	0.9	0.0001
LT SCHIRMERS 2	0.769	0.0001

LT TEAR MENISCUS HEIGHT	0.788	0.0001

P value <0.05 is statistically significant

Conjunctival impression cytology, fluorescein staining, tear break up time, Schirmer's test 1, Schirmer's test 2, and tear meniscus height of the left eye all showed a statistically significant association with dry eye.

Table 14: Pearson correlation of grading of Right Dry eye and various test

Pearson correlation	**Grading of Right Dry eye**	
	Correlation coefficient	**P value**
RT CONJUNCTIVAL IMPRESSION CYTOLOGY	0.933	0.0001
RT FLUORESCEIN STAINING	0.715	0.0001
RT Tear Break Up Time	0.811	0.0001
RT SCHIRMERS 1	0.964	0.0001
RT SCHIRMERS 2	0.640	0.0001
RT TEAR MENISCUS HEIGHT	0.766	0.0001

P value less than 0.05 is statistically significant

Conjunctival impression cytology, fluorescein staining, tear break up time, Schirmer's test 1, Schirmer's test 2, and tear meniscus height of the right eye all showed a statistically significant association with dry eye.

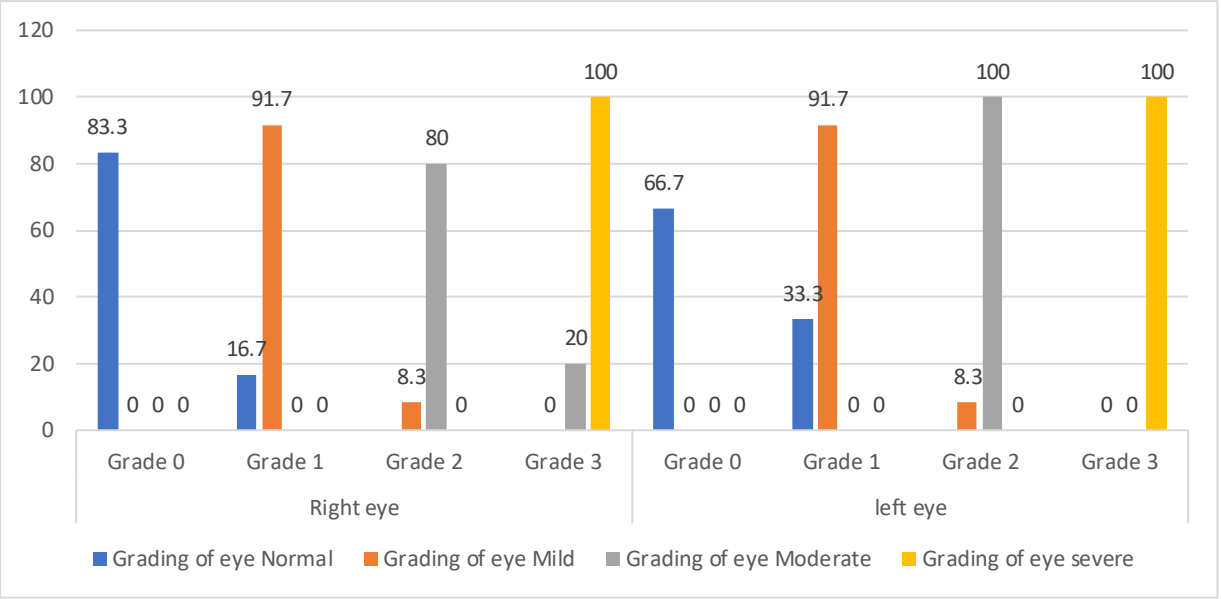
Table 15: Distribution of study participants, according to conjunctival impression cytology and grading of dry eye

Conjunctival impression cytology		**Grading of dry eye**				**P value**
		Normal	**Mild**	**Moderate**	**severe**	
Right eye	Grade 0	5(83.3%)	0	0	0	0.0001
	Grade 1	1(16.7%)	11(91.7%)	0	0	
	Grade 2	0	1(8.3%)	16(80%)	0	
	Grade 3	0	0	4(20%)	7(100%)	
Left eye	Grade 0	4(66.7%)	0	0	0	0.0001
	Grade 1	2(33.3%)	11(91.7%)	0	0	
	Grade 2	0	1(8.3%)	21(100%)	0	
	Grade 3	0	0	0	6(100%)	

Fisher exact test applied, p value <0.05 is statistically significant.

Among study participants in right eye normal eye patients, majority were grade 0 followed by grade 1, among mild dry eye patients, majority had grade 1 followed by grade 2, among moderate dry eye patients, majority had grade 2 followed by grade 3 and among severe dry eye patients, all were grade 3. In left eye normal eye patients, majority were grade 0 followed by

grade 1, among mild dry eye patients, majority had grade 1 followed by grade 2, among moderate dry eye patients, all were grade 2 and severe dry eye patients, all were grade 3. There was statistically significance between dry eye grading and conjunctival impression cytology.



DISCUSSION

6.DISCUSSION

The present study was a cross sectional study on evaluation of tear function and ocular surface changes in patients with pseudoexfoliation among department of Ophthalmology in tertiary care hospitals. The findings in our study were as follows:

Pseudoexfoliation syndrome is generalized fibrillopathy, characterized by abnormal production and accumulation of the pseudo exfoliative material in the whole body **(Streeten BW et al)** [110]

The tear film is an essential part of the lacrimal functioning unit. Holly et al. published the traditional tear film structure in 1946, which had an anterior lipid, middle aqueous, and deeper mucin layer. The modern notion is of a metastable tear film composed of an aqueous gel with mucin content decreasing from the ocular surface to the lipid layer's undersurface. Lipid comprises the superficial/outermost layer of the tear film and is predominantly produced by the meibomian glands in the eyelids, but the Moll and Zeis glands also contribute. The tear film's aqueous layer accounts for most of its thickness. It is generated by the primary lacrimal gland (reflex secretion) as well as the Krause and Wolfring auxiliary glands (basal secretion). The innermost mucin layer is generated predominantly by conjunctival goblet cells and Henle crypts in the conjunctival fornices. Mucin is also generated (secondary source) by the squamous epithelial cells of the ocular surface (cornea and conjunctiva), with a little input from the lacrimal gland. TBUT, Schirmer test I, Schirmer test II, and TMH are routinely used in the outpatient department to check the function of tear film components.

In our present study 22(48.9%) were aged >70 years, 13(28.9%) were aged 61-70 years and 10(22.2%) were aged 51-60 years. In our study the majority of patients with pseudoexfoliation were of >70 years followed by 61-70 years and 51-60 years. In a research by **Kaliaperumal et al.,**[111] individuals with pseudoexfoliation had an average age of 66.27 years, a standard deviation of 6.7 years, and a range of 55 to 80 years. In a study done by **Dermenoudi et al,** [106] the mean age among patients with pseudoexfoliation was 75.22 years with a SD of 6.4 years.

In a study done by **Vulovic et al,** [112] the mean age among patients with pseudoexfoliation was 69.2 years with a SD of 4.3 years. In a study done by **Noori et al,** [105] the mean age among patients with pseudoexfoliation was 67.9 years with a SD of 7.46 years with a range of 60 and 76 years. In a study done by **Kozobolis et al,** [113] the majority of patients with pseudoexfoliation were of >70 years followed by >80 years, 61-70 years and 51-60 years. The findings in our study were consistent with study findings of above studies.

In our present study males were 22(48.9%) and females were 23(51.1%). In a study done by **Pujar et al,** [114] males were 20(66.7%) and females were 23(33.3%). In a study done by **Dermenoudi et al,** [106] males were 28 (48.3%) and females were 30(51.7%). In a study done by **Vulovic et al,** [112] males were 26 (52%) and females were 24(48%). The findings in our study were consistent with study findings of above studies.

In our present study according to Tear Meniscus height, Right eye abnormal height was present among 25(55.6%) and Left eye abnormal height was present among 26(57.8%). In a study done by **Noori et al** [105] 100 (50.5%) eyes had Tear Meniscus height <0.35 mm whereas it was ≥ 0.35 mm in 98 (49.49%) eyes. The findings in our study were consistent with study findings of above studies. Tear Meniscus height measures tear volume, which is reduced in all types of dry eye, including mucin insufficiency, keratoconjunctivitis sicca, and meibomian gland dysfunction.

In our present study according to Schirmer's test 1, among right eye, 21(46.7%) were moderate grade, 10(22.2%) were mild grade, 8(17.8%) were normal grade and 6(13.3%) were severe grade. among left eye, 26(57.8%) were moderate grade, 8(17.8%) were normal grade 7(15.6%) were mild grade and 4(8.9%) were severe grade. According to Schirmer's test 2, among right eye abnormal test was 19(42.2%) and among left eye abnormal test was 13(28.9%). In a study done by **Noori et al,** [105] in the pseudoexfoliation group, Schirmer II value ≤ 5.5 mm was in 16 (8.08%), 182 (91.9%) eyes had Schirmer II value >10 mm and none of the eyes had Schirmer

II value between 6 and 10 mm. In our study among right and left eye majority had abnormal Schirmer's test 1 ranging from mild, moderate, severe. In a study done by **Noori et al [105],** in the pseudo exfoliation group, Schirmer I value ≤ 5.5 mm was in 12 (6.06%), 163 (82.3%) eyes had Schirmer I value >10 mm and Schirmer I value between 6 and 10 mm were in 23 (11.6%) patients. in a study done by **Pujar et al, [114]** mean Schirmer's test (mm) was 11.6 mm with a SD of 0.32 mm. in a study done by **Kaliaperumal et al, [111]** mean Schirmer's test (mm) was 10.6 mm with a SD of 7 mm. in a study done by **Gowthaman et al,[2]** according to Schirmer's test 1, 144(96%) were Normal grade, 4(2.7%) were mild grade, 2(1.3%) were moderate grade. In a study done by **Kozobolis et al, [113]** mean Schirmer's test (mm) was 12.5 mm. In a study done by **Todorovic et al, [115]** Schirmer's test (mm) was 10.8 mm with a SD of 1.28 mm. The findings in our study were consistent with study findings of above studies. In our investigation, the results of Schirmer tests I and II in the pseudo exfoliation patients were considerably lower, which we attribute to partial deposition of pseudo exfoliation material in the primary lacrimal gland and its ducts. The Schirmer test II evaluates the sufficiency of basal secretion of the aqueous component of the tear film, which is diminished in pseudo exfoliation patients. This decrease in basal aqueous humour might be linked to the deposition of pseudoexfoliation material and changes in the shape of the glands of Krause and Wolfring .

In our present study according to Tear Break Up Time, among right eye, 20(44.4%) were moderate grade, 18(40%) were severe grade and 7(15.6%) were mild grade. Among the left eye, 21(46.7%) were moderate grade, 16(35.6%) were severe grade and 8(17.8%) were mild grade. In our study among right and left eye majority had abnormal Tear Break Up Time ranging from mild, moderate, severe. Tear Break Up Time was lower among pseudo exfoliation patients. In a study by **Pujar et al, [114]** mean Tear Break Up Time was 7.8 sec with a SD of 0.5 sec. In a study done by **Kaliaperumal et al, [111]** mean Tear Break Up Time was 6.4 sec. In a study done by **Gowthaman et al,[2]** according to Tear Break Up Time, 147(98%) were Normal

grade, 3(2%) were mild grade. In a study done by **Erdogan et al,** [102] Tear Break Up Time was 7.3 sec with a SD of 4.8 sec. In a study done by **Skergro et al,** [107] found a statistically significant difference in every component between groups, most prominent in tear film break up time test. Patients with pseudoexfoliation influence tear secretion and stability possibly related with conjunctival involvement in the condition. In a study done by **Todorovic et al,** [115] mean Tear Break Up Time was 5.19 sec with a SD of 1.23 sec. In a study done by **Noori et al,** [105] in the pseudo exfoliation group, 125 (63.1%) eyes had TBUT ≤10s, >10s in 73 (36.9%) eyes. Mean Tear Break Up Time was 9.7 sec with a SD of 5.5 sec. The findings in our study were consistent with study findings of above studies. TBUT evaluates the sufficiency of the tear film's mucin layer, which is decreased in patients with pseudoexfoliation. This deficiency, we hypothesise, is due to the deposition of pseudoexfoliation material at the mouths of the goblet cells, which reduces mucin production.

In our present study, according to Fluorescein staining, among right eye abnormal tests was 9(20%) and among left eye abnormal tests was 8(17.8%). In a study done by **Dermenoudi et al,** [106] mild corneal fluorescein staining was present among 32.8%, moderate grade among 31% and severe grade among 29.3%.

In our present study according to Conjunctival impression cytology, in right eye, 17(37.8%) were grade 2, 12(26.7%) were grade 1, 11(24.4%) were grade 3 and 5(11.1%) were grade 0. In Left eye, 22(48.9%) were grade 2, 13(28.9%) were grade 1, 6(13.3%) were grade 3 and 4(8.9%) were grade 0. In a study done by **Kaliaperumal et al,** [111] Stage 1 was among 66.7%, Stage 2 was among 33.3%, which was significantly lower when compared to the pseudoexfoliation group. In a study done by **Erdogan et al,** [102] among pseudoexfoliation groups, 21(43.8%) were grade 2, 9(18.7%) were grade 1, 15(31.2%) were grade 3 and 3(6.3%) were grade 0. In a study done by **Dermenoudi et al,** [106] 46.6% had mild Conjunctival Fluorescein staining, 16.4% were normal Conjunctival Fluorescein staining, 24.1% had Moderate Conjunctival Fluorescein

staining, 12.9% had Severe Conjunctival Fluorescein staining. The findings in our study were consistent with study findings of above studies.

In our present study according to Grading of dry eye, in right eye, 20(44.4%) were moderate grade, 12(26.7%) were mild grade, 7(15.6%) were severe grade and 6(13.3%) were normal grade. in Left eye, 21(46.7%) were moderate grade, 12(26.7%) were mild grade, 6(13.3%) were severe grade and 6(13.3%) were normal grade. In a study done by **Gowthaman et al,[2]** the prevalence of dry eyes among patients with pseudoexfoliation was 9(6%). OSDI (Ocular surface Disease Index) – 12 item questionnaire was used to evaluate symptoms associated with dry eye. OSDI score was calculated using the formula, ranged from 0-100. Score above 25 was considered as a dry eye.

In our present study, according to the OSD score, moderate dry eye was among 20(44.4%), mild dry eye was among 12(26.7%), severe dry eye was among 7(15.6%) and normal eye was among 6(13.3%). In a study done by **Dermenoudi et al, [106]** according to the OSD score, severe dry eye was among 36.2% and normal eye was among 29.3%, mild dry eye was among 22.4% and moderate dry eye was among 12.1%. In a study done by **Todorovic et al, [105]** mean OSD score was 29.18 with a SD of 3.01. The findings in our study were consistent with study findings of above studies.

Conjunctival impression cytology, fluorescein staining, tear break up time, Schirmer's test 1, Schirmer's test 2, and tear meniscus height all showed a statistically significant link with dry eye in the current investigation.There was statistically significance between dry eye grading and conjunctival impression cytology.

It should be noted that, although aqueous layer tests in patients with PEXS may be normal, they tend to be lower than those in healthy persons, and this should be considered when choosing medicine to treat PEX glaucoma.[92] **Oncel et al[116]** established that tear film osmolarity was higher in patients with PEX, which can be explained by the dysfunction of the goblet

conjunctival cells. Ina study done by **Vulvonic et al,** [112] TBUT test results from our study recorded lower in patients with PEX compared with control group patients with statistically significant difference. We may advise the ophthalmologist that anti-glaucomatous medications should be considered for the treatment of glaucoma due to their unfavorable impact on the damaged ocular surface produced by the disrupted tear film. Because of its deleterious influence on the conjunctival goblet cells, PEX is the primary cause of tear film instability.

CONCLUSION

7.CONCLUSION

According to our study using conjunctival impression cytology and tear film tests, patients with pseudoexfoliation syndrome are more likely to develop dry eye because it results in abnormalities in the tear film and a decrease in the number of goblet cells .More research is required to ascertain the precise intricacies of how PEX modifies the morphology of GC.

SUMMARY

8.SUMMARY

In our study the majority of patients with pseudoexfoliation were of >70 years followed by 61-70 years and 51-60 years.In our present study males were 22(48.9%) and females were 23(51.1%).

In our present study according to Tear Meniscus height, Right eye abnormal height was present among 25(55.6%) and Left eye abnormal height was present among 26(57.8%). In our present study according to Schirmer's test 1, among right eye, 21(46.7%) were moderate grade, 10(22.2%) were mild grade, 8(17.8%) were normal grade and 6(13.3%) were severe grade. Among the left eye, 26(57.8%) were moderate grade, 8(17.8%) were normal grade 7(15.6%) were mild grade and 4(8.9%) were severe grade.According to Schirmer's test 2, the right eye abnormal test was 19(42.2%) and the left eye abnormal test was 13(28.9%).

In our present study according to Tear Break Up Time, among the right eye, 20(44.4%) were moderate grade, 18(40%) were severe grade and 7(15.6%) were mild grade. Among the left eye, 21(46.7%) were moderate grade, 16(35.6%) were severe grade and 8(17.8%) were mild grade.

In our present study, according to Fluorescein staining, among right eye abnormal tests was 9(20%) and among left eye abnormal tests was 8(17.8%).In our present study according to Conjunctival impression cytology, in the right eye, 17(37.8%) were grade 2, 12(26.7%) were grade 1, 11(24.4%) were grade 3 and 5(11.1%) were grade 0. in Left eye, 22(48.9%) were grade 2, 13(28.9%) were grade 1, 6(13.3%) were grade 3 and 4(8.9%) were grade 0.

In our present study, according to Grading of dry eye, in the right eye, 20(44.4%) were moderate grade, 12(26.7%) were mild grade, 7(15.6%) were severe grade and 6(13.3%) were normal grade. in Left eye, 21(46.7%) were moderate grade, 12(26.7%) were mild grade, 6(13.3%) were severe grade and 6(13.3%) were normal grade.

In our present study, according to the OSD score, moderate dry eye was among 20(44.4%), mild dry eye was among 12(26.7%), severe dry eye was among 7(15.6%) and normal eye was among 6(13.3%).

Conjunctival impression cytology, fluorescein staining, tear break up time, Schirmer's test 1, Schirmer's test 2, and tear meniscus height all showed a statistically significant link with dry eye in the current investigation. The relationship between conjunctival impression cytology and dry eye grading was statistically significant.

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ANNEXURES

ANNEXURE-I

CASE PROFORMA

Name:	Case No:
Age:	Date:
Sex:	1P No:
Occupation:	DOE:
Address:	

Chief complaints:

Sl No	Complaints	Yes/ No	Duration
1	Foreign body sensation		
2	Itching		
3	Photophobia		
4	Watering of eye		
5	Blurred vision		
6	Injury		
7	Prolonged use of topical drugs		
8	Others		

Past history:

DM / HTN / BA / Epilepsy

Family history:

Personal history:

Appetite – Sleep – Bowel –

Diet – Habits – Bladder –

GPE:

Pallor / Edema /Icterus / Cyanosis / Clubbing / Lymphadenopathy

Vital signs:

a. Pulse – c) RR –

b. BP – d) Temp –

Systemic examination:

a. CVS – c. RS –

b. PA – d. CNS –

OCULAR EXAMINATION		
	RE	**LE**
1. HEAD POSTURE 2. OCULAR POSTURE 3. FACIAL SYMMETRY		
4. OCULAR MOVEMENTS		
5. VISUAL ACUITY: a) Distant b) Near		

6. ANTERIOR SEGMENT		
7. FUNDUS (IDO & Slit Lamp +90D)		
8. INTRAOCULAR PRESSURE		
9. DRY EYE TESTS a. Tear meniscus height (mm) b. Schirmer's test I (mm) c. Schirmer's test II (mm) d. TBUT (sec) e. Conjunctival staining f. Corneal staining		
10. OSDI score		
11. Conjunctival impression cytology grade		

ANNEXURE- II

PATIENT INFORMATION SHEET

TITLE: ''EVALUATION OF TEAR FUNCTION AND OCULAR SURFACE CHANGES IN PATIENTS WITH PSEUDOEXFOLIATION"

This information is to help you understand the purpose of the study "**Evaluation of tear function and ocular surface changes in patients with pseudoexfoliation**"

You are invited to take part voluntarily in this research study, it is important that you read and understand purpose, procedure, benefits and discomforts of the study.

To find frequency, severity and grade of dry eye disease in patients with pseudoexfoliation syndrome.

There are no risks associated with the various investigations to be done which includes slit lamp examination, Schirmers test, Tear film break up time, Tear meniscus height.

Participation in this research study may not change the final outcome of your eye condition. However, patients in the future may benefit as a result of knowledge gained from this study. You will not be charged extra for any of the procedures performed during the research study. Your taking part in this study is entirely voluntary.

You may refuse to take part in the study or you may stop your participation in the study at any time, without any penalty or loss of any benefits to which you were otherwise entitled before taking part in this study.

CONFIDENTIALITY

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available. Your original records may be reviewed by your doctor or ethics review board. For further information,/clarification please contact Dr. MANJULA. T, SRI

DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR – 563101.Contact no: 9561602115 to Dr. Swati Kushwah

DOCTOR'S DETAILS:

DR. MANJULA. T

MBBS, MS

PROFESSOR

DEPARTMENT OF OPHTHALMOLOGY,

SDUMC, KOLAR – 563101

ಶ್ರೀದೇವರಾಜ್ಅರಸ್ಉನ್ನತಶಿಕ್ಷಣಮತ್ತುಸಂಶೋಧನಾಸಂಸ್ಥೆ,

ಟಮಕ, ಕೋಲಾರ - 563101.

ಶೀರ್ಷಿಕೆ:"ಕಣ್ಣೀರಿನ ಕಾರ್ಯಮತ್ತು ಆಕ್ಯುಲರ್ ಮೇಲ್ಮೈ ಬದಲಾವಣೆಗಳು ಮತ್ತು ಸ್ಯೂಡೋಎಕ್ಸ್ಫೋಲಿಯೇಶನ್ ಹೊಂದಿರುವ ರೋಗಿಗಳಲ್ಲಿ ನವಿರು ಮೇಲ್ಮೈ ಬದಲಾವಣೆಗಳು"

ಈ ಮಾಹಿತಿಯು ಅಧ್ಯಯನದ ಉದ್ದೇಶವನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳಲು ನಿಮಗೆ ಸಹಾಯ ಮಾಡುತ್ತದೆ "
ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಭಾಗವಹಿಸಲು ನಿಮ್ಮನ್ನು ಆಹ್ವಾನಿಸಲಾಗಿದೆ, ನೀವು ಹೇಳಿದ ಮತ್ತು ಉದ್ದೇಶವನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳುವುದು ಬಹಳ ಮುಖ್ಯ,
ಕಾರ್ಯವಿಧಾನದ ಪ್ರಯೋಜನಗಳು
ಸ್ಯೂಡೋಎಕ್ಸ್ಫೋಲಿಯೇಶನ್ ರೋಗಿಗಳಲ್ಲಿ ಒಣ ಕಣ್ಣಿನ ಕಾಯಿಲೆಯ ತೀವ್ರತೆ ಮತ್ತು ದರ್ಜೆಯನ್ನು ಕಂಡುಹಿಡಿಯಲು.
ಖಂಡಿತವಾಗಿಯೂ ಮಾಡಬೇಕಾದ ತನಿಖೆಯೊಂದಿಗೆ ಯಾವುದೇ ಅಪಾಯಗಳು ಸಂಬಂಧಿಸಿಲ್ಲ
ನಾವು ಸ್ಕಿರ್ಮರ್ಸ್ ಪರೀಕ್ಷೆ, ಕಣ್ಣೀರಿನ ಚಲನಚಿತ್ರವು ಸಮಯವನ್ನು ಮುರಿಯುತ್ತದೆ.
ಅಂತಹ ತೊಡಕುಗಳನ್ನು ಅವನು ಗುರುತಿಸುವುದು ಅಥವಾ ಅಭಿವೃದ್ಧಿ ಹೊಂದುವ ಅಪಾಯವು ಅದರ ಸಂಭವವನ್ನು ಕಡಿಮೆ ಮಾಡಲು ಬೇಕಾದ ಬದಲಾವಣೆಗಳ ನಿರ್ಣಯದಲ್ಲಿ ಮಹತ್ವದ್ದಾಗಿರುತ್ತದೆ, ಹೀಗಾಗಿ ತೀವ್ರವಾದ ಆಕ್ಯುಲರ್ ಆವಿಷ್ಕಾರದ ಹೊರೆಯನ್ನು ಕಡಿಮೆ ಮಾಡುತ್ತದೆ ನಮ್ಮ ವೀಕ್ಷಣೆ ಸಹ ಪ್ರಾಮುಖ್ಯತೆಯನ್ನು ಹೊಂದಿರಬಹುದು
ಈಅಧ್ಯಯನದಲ್ಲಿನಿಮ್ಮಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯುಸಂಪೂರ್ಣವಾಗಿಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ.ಅಧ್ಯಯನದಲ್ಲಿಪಾಲ್ಗೊಳ್ಳಲುನೀವುನಿರಾಕರಿಸಬಹುದುಅಥವಾಈಅಧ್ಯಯನದಲ್ಲಿಪಾಲ್ಗೊಳ್ಳುವುದಕ್ಕಿಂತಮೊದಲುನೀವುಯಾವುದೇಅರ್ಹತೆಗೆಯಾವುದೇದಂಡವಿಲ್ಲದೆಅಥವಾನಷ್ಟವಿಲ್ಲದೆಯೇಯಾವುದೇಸಮಯದಲ್ಲಿಯಾವುದೇಸಮಯದಲ್ಲಿಭಾಗವಹಿಸುವಿಕೆಯನ್ನುನಿಲ್ಲಿಸಬಹುದು. ಈ ಸಂಶೋಧನೆಯಿಂದ ಹೊರಬರುವ ಮಾಹಿತಿಯನ್ನು ವೈದ್ಯರು ಯಾವುದೇ ಕಾನ್ಫರೆನ್ಸ್ನಲ್ಲಿ ಪ್ರಕಟಿಸಲು ಅನುಮತಿ ಸೂಚಿಸಿರುತ್ತೇನೆ

<u>ಗೌಪ್ಯತೆ</u>

ನಿಮ್ಮ ವೈದ್ಯಕೀಯ ಮಾಹಿತಿಯನ್ನು ಅಧ್ಯಯನದ ವೈದ್ಯರು ಮತ್ತು ಸಿಬ್ಬಂದಿ ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಸಾರ್ವಜನಿಕವಾಗಿಲಭ್ಯವಿರುವುದಿಲ್ಲ.ನಿಮ್ಮಮೂಲದಾಖಲೆಗಳನ್ನು ನಿಮ್ಮ ವೈದ್ಯರು ಅಥವಾ ನೈತಿಕ ವಿಮರ್ಶೆ ಮಂಡಳಿ ಪರಿಶೀಲಿಸಬಹುದು.

<u>ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ</u>

ಡಾ. ಮಂಜುಳ .ಟಿ. ಆರ್

<u>ಎಸ್ ಡಿ ಯು ಎಮ್ ಸಿ.</u>

ಟಮಕ, ಕೋಲಾರ

ಸಂಪರ್ಕ ಸಂಖ್ಯೆ: 9886591772

ಇ-ಮೇಲ್ drmanjulamims@gmail.com

ANNEXURE- III

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR - 563101.

INFORMED CONSENT FORM

Case no:

IP no:

TITLE: EVALUATION OF TEAR FUNCTION AND OCULAR SURFACE CHANGES IN PATIENTS WITH PSEUDOEXFOLIATION

I, the undersigned, agree to participate in this study and authorize the collection and disclosure of personal information as outlined in this consent form.

I understand the purpose of this study, the risks and benefits of the technique and the confidential nature of the information that will be collected and disclosed during the study. The information collected will be used only for research.

I have had the opportunity to ask questions regarding the various aspects of this study and my questions have been answered to my satisfaction.

I understand that I remain free to withdraw the participation from this study at any time and this will not change the future care.

Participation in this study does not involve any extra cost to me.

Name	Signature	Date	Time
Patient:			
Witness:			
Primary Investigator/ Doctor:			

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH,
TAMAKA, KOLAR – 563101

ತಿಳಿವಳಿಕೆಸಮ್ಮತಿನಮೂನೆ

ಶೀರ್ಷಿಕೆ: "ಕಣ್ಣೀರಿನ ಕಾರ್ಯಮತ್ತು ಆಕ್ಯುಲರ್ ಮೇಲ್ಮೈ ಬದಲಾವಣೆಗಳು ಮತ್ತು ಸ್ಯೂಡೋಎಕ್ಸ್ಫೋಲಿಯೇಶನ್

ಹೊಂದಿರುವ ರೋಗಿಗಳಲ್ಲಿ ನವಿರು ಮೇಲ್ಮೈ ಬದಲಾವಣೆಗಳು"

ಈ ಸಂಶೋಧನೆಗೆ ರೋಗಿಯ ಗುರುತಿನ ಸಂಖ್ಯೆ:

ಐಪಿ ಸಂಖ್ಯೆ:

ಅಂಗೀಕರಿಸಿದ ನಾನು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ ಮತ್ತು ಈ ಸಮ್ಮತಿಯ ರೂಪದಲ್ಲಿ ವಿವರಿಸಿರುವಂತೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯನ್ನು ದೃಢೀಕರಿಸುತ್ತೇನೆ.

ನಾನು ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ತಂತ್ರಗಳ ಅಪಾಯಗಳು ಮತ್ತು ಪ್ರಯೋಜನಗಳನ್ನು ಮತ್ತು ಅಧ್ಯಯನದಲ್ಲಿಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವ ಮಾಹಿತಿಯ ಗೌಪ್ಯತೆಗೆ ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಸಂಶೋಧನೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ.

ಈ ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳನ್ನು ಕುರಿತು ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶವಿದೆ ಮತ್ತು ನನ್ನ ತೃಪ್ತಿಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ಉತ್ತರ ನೀಡಲಾಗಿದೆ.

ಈ ಸಂಶೋಧನೆಯಿಂದ ಹೊರಬರುವ ಮಾಹಿತಿಯನ್ನು ವೈದ್ಯರು ಯಾವುದೇ ಜರ್ನಲ್ನಲ್ಲಿ ಅಥವಾ ಕಾನ್ಫೆರೆನ್ಸ್ನಲ್ಲಿ ಪ್ರಕಟಿಸಲು ಅನುಮತಿ ಸೂಚಿಸಿರುತ್ತೇನೆ

ನಾನು ಈ ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂತೆಗೆದುಕೊಳ್ಳಲು ಮುಕ್ತವಾಗಿರುತ್ತೇನೆ ಮತ್ತು ಇದು ನನ್ನ ಮುಂದಿನ ಕಾಳಜಿಯನ್ನು ಬದಲಿಸುವುದಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಈ ಸಂಶೋಧನಾ ಯೋಜನೆಯ ಭಾಗವಹಿಸುವಿಕೆ ನನಗೆ ಯಾವುದೇ ಹಣಕಾಸಿನ ಹೊರೆ ಒಳಗೊಂಡಿರುವುದಿಲ್ಲ.

ಹೆಸರು	ಸಹಿ	ದಿನಾಂಕ	ಸಮಯ
ರೋಗಿಯ:			
ಸಾಕ್ಷಿ 1:			
ಸಾಕ್ಷಿ 2:			
ಪ್ರಾಥಮಿಕ ತನಿಖೆದಾರ / ಡಾಕ್ಟರ್:			

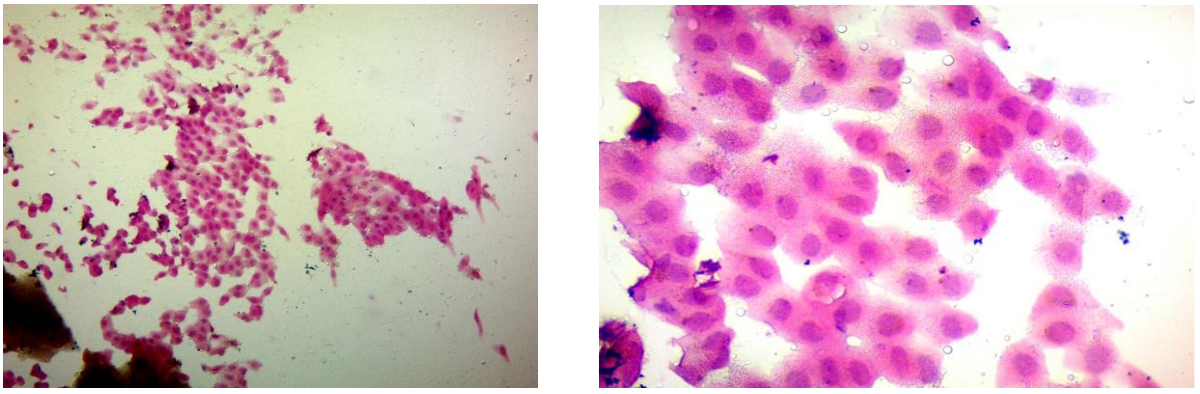
ANNEXURE- IV

PHOTOGRAPHS

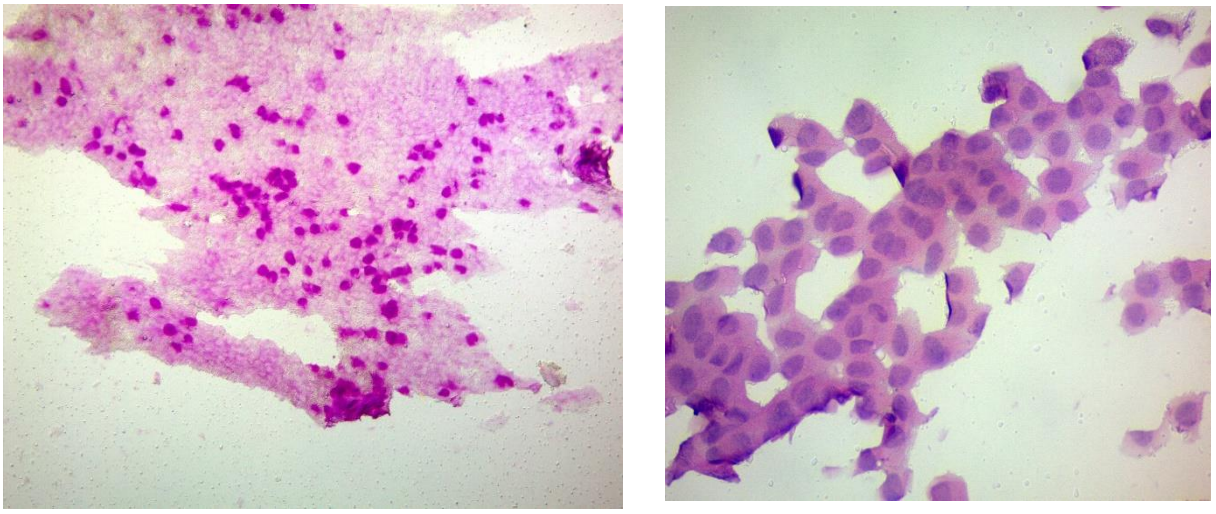
PHOTOGRAPH 1: SCHIRMER'S TEST

PHOTOGRAPH 2: TEAR FILM BREAK UP TIME

PHOTOGRAPH 3: CONJUNCTIVAL SAMPLE COLLECTION FOR CONJUNCTIVAL IMPRESSION CYTOLOGY



PHOTOGRAPH 3: CONJUNCTIVAL IMPRESSION CYTOLOGY PAS STAINING (10 X and 40 X)



PHOTOGRAPH 4: CONJUNCTIVAL IMPRESSION CYTOLOGY PAS STAINING and H &E SATINING (10 X and 40 X)

KEY TO MASTER CHART

ST - SCHIRMER'S TEST

TBUT - TEAR FILM BREAK UP TIME

FS - FLOURESCEIN STAINING

TMH - TEAR MENISCUS HEIGHT

CIC - CONJUNCTIVAL IMPRESSION CYTOLOGY

OSDI - OCULAR SURFACE DISEASE INDEX

MASTER CHART

SL NO	UHID NO	AGE	GENDER	TEAR MENISCUS HEIGHT (mm)		SCHIRMERS 1 (mm)		SCHIRMERS 2 (mm)		T BUT (sec)		FLUORESCEIN STAINING		CONJUNCTIVAL IMPRESSION CYTOLOGY		OSD INDEX	GRADING OF DRY EYE	
				RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE		RE	LE
1	89887	67 Y	F	ABNORMAL	ABNORMAL	8	9	5	5	4	5	5	5	GRADE 2	GRADE 2	28	MODERATE	MODERATE
2	89872	56 Y	M	NORMAL	NORMAL	12	14	8	8	12	12	1	2	GRADE 1	GRADE 1	12	NORMAL	NORMAL
3	92139	76 Y	M	ABNORMAL	ABNORMAL	9	7	5	4	7	7	6	6	GRADE 2	GRADE 2	24	MODERATE	MODERATE
4	92131	66 Y	F	NORMAL	NORMAL	10	10	5	6	9	9	3	4	GRADE 2	GRADE 2	14	MILD	MILD
5	115128	52 Y	F	NORMAL	NORMAL	10	10	6	5	10	10	4	3	GRADE 1	GRADE 1	18	MILD	MILD
6	101126	87 Y	M	ABNORMAL	ABNORMAL	6	7	4	3	5	5	6	6	GRADE 3	GRADE 2	30	MODERATE	MODERATE
7	45943	77 Y	F	ABNORMAL	ABNORMAL	6	6	5	4	6	5	7	7	GRADE 2	GRADE 2	32	MODERATE	MODERATE
8	76885	89 Y	M	NORMAL	NORMAL	12	12	10	10	14	14	2	2	GRADE 0	GRADE 1	12	NORMAL	NORMAL
9	132960	55 Y	F	ABNORMAL	ABNORMAL	7	8	6	5	6	6	6	6	GRADE 2	GRADE 2	30	MODERATE	MODERATE
10	83295	78 Y	M	NORMAL	NORMAL	10	10	6	6	9	9	4	4	GRADE 1	GRADE 1	14	MILD	MILD
11	101041	67 Y	F	NORMAL	NORMAL	10	10	8	8	10	10	5	5	GRADE 1	GRADE 1	15	MILD	MILD
12	127280	85 Y	M	ABNORMAL	ABNORMAL	4	4	4	4	3	3	8	8	GRADE 3	GRADE 3	38	SEVERE	SEVERE
13	96169	69Y	F	ABNORMAL	ABNORMAL	3	4	4	4	4	3	8	8	GRADE 3	GRADE 3	40	SEVERE	SEVERE
14	115167	54 Y	F	NORMAL	NORMAL	10	10	5	6	9	10	4	4	GRADE 1	GRADE 1	20	MILD	MILD
15	128241	88 Y	M	ABNORMAL	ABNORMAL	8	7	5	4	7	7	7	7	GRADE 2	GRADE 2	25	MODERATE	MODERATE
16	130294	54 Y	F	ABNORMAL	ABNORMAL	8	9	6	4	5	6	6	6	GRADE 3	GRADE 2	30	MODERATE	MODERATE
17	101127	88 Y	F	NORMAL	NORMAL	10	10	6	5	9	10	4	4	GRADE 1	GRADE 1	14	MILD	MILD
18	72856	77 Y	M	NORMAL	ABNORMAL	8	9	5	4	6	5	6	7	GRADE 2	GRADE 2	28	MODERATE	MODERATE
19	83739	53 Y	M	ABNORMAL	ABNORMAL	3	4	3	4	3	4	7	7	GRADE 3	GRADE 3	34	SEVERE	SEVERE
20	130051	75 Y	F	NORMAL	NORMAL	10	9	9	9	10	9	4	4	GRADE 1	GRADE 1	22	MILD	MILD
21	125268	67 Y	M	ABNORMAL	ABNORMAL	9	8	5	4	8	8	6	6	GRADE 2	GRADE 2	26	MODERATE	MODERATE
22	62643	78 Y	F	NORMAL	NORMAL	12	11	8	8	12	14	2	2	GRADE 0	GRADE 0	10	NORMAL	NORMAL
23	104806	89 Y	F	ABNORMAL	ABNORMAL	4	3	4	4	3	4	9	9	GRADE 3	GRADE 3	35	SEVERE	SEVERE
24	86214	66 Y	F	ABNORMAL	ABNORMAL	10	9	6	5	10	9	4	5	GRADE 1	GRADE 1	18	MILD	MILD
25	115019	89 Y	F	ABNORMAL	ABNORMAL	8	7	5	4	5	5	7	7	GRADE 2	GRADE 2	30	MODERATE	MODERATE
26	130789	55 Y	F	ABNORMAL	ABNORMAL	5	8	5	4	5	7	6	7	GRADE 3	GRADE 2	32	MODERATE	MODERATE
27	116333	67 Y	F	ABNORMAL	ABNORMAL	3	4	3	4	4	3	8	8	GRADE 3	GRADE 3	45	SEVERE	SEVERE
28	104791	79 Y	M	ABNORMAL	ABNORMAL	5	8	5	4	6	5	6	6	GRADE 2	GRADE 2	30	MODERATE	MODERATE
29	109105	90 Y	M	ABNORMAL	ABNORMAL	6	6	5	4	4	4	7	7	GRADE 2	GRADE 2	31	MODERATE	MODERATE
30	122815	77 Y	F	NORMAL	NORMAL	12	11	7	8	12	11	1	1	GRADE 0	GRADE 0	10	NORMAL	NORMAL
31	115009	68 Y	M	ABNORMAL	ABNORMAL	8	9	5	4	3	4	6	6	GRADE 2	GRADE 2	24	MODERATE	MODERATE
32	80336	59 Y	F	ABNORMAL	ABNORMAL	6	5	5	5	5	6	7	7	GRADE 2	GRADE 2	27	MODERATE	MODERATE
33	104958	70 Y	M	ABNORMAL	ABNORMAL	5	7	4	5	7	8	7	6	GRADE 2	GRADE 2	25	MODERATE	MODERATE
34	86795	83 Y	M	NORMAL	NORMAL	10	11	6	5	10	9	4	4	GRADE 1	GRADE 1	20	MILD	MILD
35	94659	55 Y	F	NORMAL	NORMAL	11	10	5	6	9	10	3	4	GRADE 1	GRADE 1	16	MILD	MILD
36	105094	88 Y	M	ABNORMAL	ABNORMAL	4	5	4	4	3	4	8	8	GRADE 3	GRADE 3	46	SEVERE	SEVERE
37	127757	63 Y	F	ABNORMAL	ABNORMAL	8	7	6	5	6	7	6	6	GRADE 2	GRADE 2	30	MODERATE	MODERATE
38	115185	72 Y	M	NORMAL	NORMAL	10	10	5	6	10	11	4	4	GRADE 1	GRADE 1	15	MILD	MILD
39	789951	89 Y	F	ABNORMAL	ABNORMAL	8	9	4	5	6	5	7	7	GRADE 2	GRADE 2	27	MODERATE	MODERATE
40	747223	56 Y	M	NORMAL	NORMAL	12	15	9	10	12	14	2	2	GRADE 0	GRADE 0	10	NORMAL	NORMAL
41	837612	62 Y	M	ABNORMAL	ABNORMAL	6	5	5	4	7	5	6	6	GRADE 2	GRADE 2	28	MODERATE	MODERATE
42	136836	76 Y	M	NORMAL	NORMAL	10	9	6	5	10	9	3	3	GRADE 1	GRADE1	16	MILD	MILD
43	837112	65 Y	M	ABNORMAL	ABNORMAL	9	8	4	3	5	6	6	6	GRADE 3	GRADE 2	27	MODERATE	MODERATE
44	862143	77 Y	F	NORMAL	NORMAL	12	14	8	10	12	11	2	2	GRADE 0	GRADE 0	10	NORMAL	NORMAL
45	116323	64 Y	M	ABNORMAL	ABNORMAL	3	4	4	3	5	4	9	9	GRADE 3	GRADE 3	45	SEVERE	SEVERE