“A ONE YEAR CROSS SECTIONAL STUDY OF PREVALENCE OF DRY EYES IN TYPE 2 DIABETICS”

REG NO. BK0110002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. S.

in

OPHTHALMOLOGY

**DEPARTMENT OF OPHTHALMOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"A ONE YEAR CROSS SECTIONAL STUDY OF PREVALENCE OF DRY EYES IN TYPE 2 DIABETICS"** is a bonafide research work done by **CANDIDATE REGISTER NO. BK0110002**

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LIST OF ABBREVIATIONS USED

ADA	-	American diabetes association
CSME	-	Clinically significant macular edema
CWS	-	Cotton wool spots
DM	-	Diabetes Mellitus
ETDRS	-	Early treatment diabetic retinopathy study
H&E	-	Haematoxylin and eoisinophilic stain
IDDM	-	Insulin dependent diabetes mellitus
IRMA	-	Intraretinal microvascular abnormalties
KCS	-	Keratoconjunctivitis sicca
MA	-	Microaneurysms
N:C	-	Nuclear cytoplasmic ratio
NIIDM	-	Non insulin dependent diabetes mellitus
NPDR	-	Non proliferative diabetic retinopathy
NVD	-	Neovascularization at the disc
NVE	-	Neovascularization elsewhere
PAS	-	Periodic acid Schiff
PDR	-	Proliferative diabetic retinopathy
PRP	-	Pan retinal photocoagulation
SPK	-	Superficial punctate keratitis
ST	-	Schirmers test
TBUT	-	Tear film break up time

ABSTRACT

Background and Objective

Diabetes is often associated with several significant ocular conditions, such as retinopathy, refractive changes, cataract, nerve palsies, glaucoma and macular edema. However, recently problems involving ocular surface disorders, dryness in particular had been reported. This present study was an attempt to find out the prevalence of dry eyes in patients of type 2 diabetes and also to study the association of dry eyes with the duration of disease and with the stages of diabetic retinopathy.

Methods

The present one year cross-sectional study was conducted on a total of 117 patients diagnosed with type 2 diabetes mellitus in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

Results

In the present study majority of the patients (76.07%) were males with male to female ratio of 3.17:1. Most of the patients (31.62%) were aged more than 60 years followed by 56 to 60 (19.66%). Overall, the mean age was 56.44 ± 9.10 years. More than half (56.41%) patients had duration of diabetes upto five years. Overall, mean duration was 7.00 ± 6.77 years In the present study the Schirmer's test, tear film break up time, Rose Bengal staining and conjunctival impression cytology was positive among 43.59%, 43.59%, 20.51% and 37.61% of patients respectively.

Conclusion and interpretation

The results of the present study showed 44.44% prevalence of dry eye syndrome among patients with type 2 diabetes mellitus. Dry eye syndrome in patient with type 2 diabetes mellitus was significantly associated with increasing age and longer duration whereas diabetic retinopathy and male and female ratio did not influence the prevalence of dry eye syndrome.

Key Words: Conjunctival impression cytology; Diabetes mellitus; Dry eye syndrome; Non proliferative diabetic retinopathy; Rose Bengal test; Schirmer's test; Tear film break up time;

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Chapter 1

Introduction

INTRODUCTION

Diabetes is one of the most common leading cause of blindness in 20–74 year old people.[1] It is quickly emerging as one of the biggest health-related catastrophes the world has ever witnessed.[2] The problem is not exclusive to the United States. The World Health Organization (WHO) estimates that there will be 370 million people with diabetes on the planet by 2030, which is nearly twice the figure reported in 2000.[3] Furthermore, the treatment cost on medications and testing equipment for diabetes in the United States are overwhelming.[4]

Diabetes is often associated with several significant ocular conditions, such as retinopathy, refractive changes, cataract, nerve palsies, glaucoma and macular edema. However, recently problems involving ocular surface, dryness in particular had been reported.[5]

The most common dry eye symptoms reported by patients with diabetes are burning and foreign body sensation.[10,11] Corneal complications include superficial punctate keratopathy, corneal ulcerations and persistent epithelial defects.

There are several theories that might explain the connection between dry eye and diabetes. The most frequently cited associated factors include peripheral neuropathy secondary to hyperglycemia, insulin insufficiency, inflammation,[5] development of autonomic dysfunction and the involvement of the enzyme aldose reductase in the sorbitol pathway.[12,13] A more recent mouse study showed diabetes-induced histological alterations in the lacrimal gland, suggesting that

hyperglycemia-related oxidative stress may play a role in diabetic dry eye syndrome.[14]

A review of the literature finds that more than half of patients with diabetes likely have dry eye disease.[6,7] One study indicated that nearly 53% of people with diabetes experienced dry eye symptoms.[7] The authors of another study corroborated this evidence and noted that 54.3% of patients with diabetes suffered from ocular dryness.[8] One additional study documented reduced Schirmer's score in patients with diabetes.[9]

Diabetic patients more than 40 years are more prone to get dry eye syndrome, diabetic retinopathy, diabetic nephropathy and peripheral neuropathy. These complications can be prevented by diagnosing and controlling diabetes in a early stage.

The early diagnosis of dry eye syndrome in diabetic patients is important for beginning of treatment. Nevertheless studies to evaluate the prevalence of dry eye syndrome in type 2 diabetic patients are lacking and there is scarcity of studies relating to prevalence of dry eyes and ocular surface disorders in diabetic patients in Indian context.

Hence the present study was undertaken to assess the prevalence of dry eyes in patients with type 2 diabetes and also to study the association of dry eyes with the duration of disease and with the stages of diabetic retinopathy.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

Primary

To know the prevalence of dry eyes in patients with type 2 diabetes.

Secondary

To study the association of dry eyes with the duration of disease and with the stages of diabetic retinopathy.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Our knowledge of dry eye dates back to the clinical description of French dermatologist Gougerot, who described the occurrence of atrophy of the salivary and conjunctival glands in a group of middle-aged women.[15] The defining work of Swedish ophthalmologist Henrick S. C. Sjogren in 1933, established the term Keratoconjunctivitis sicca (KCS) and attributed the dryness and symptoms of dry eye to a reduction of the aqueous component of the tears. He also documented the association of keratoconjunctivitis sicca with xerostomia and rheumatoid arthritis in his original thesis Zur Kenntnis keratoconjunctivitis sicca.[16]

The rudimentary view that dry eye is simply a deficiency of tear fluid has evolved into an appreciation of dry eye as a disturbance in the complex interaction of the tear film, ocular surface, and lacrimal glands that is conditioned by hormonal support.[17] Disturbance of this homeostatic balance produces inflammation of the lacrimal tissue and the ocular surface, with subsequent damage to the ocular surface.

The modern definition of dry eye disease is based on the concept of the three layers of the tear film devised by Holly and Lemp[18] adopted by the National workshop on dry eyes.

Dry eye is defined as “a disorder of the tear film due to tear deficiency or excessive evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort”.

Normal physiology of tear film

The tear film is a vital and a dynamic structure that is not only produced by, but also affects, the adjacent living tissue and organisms. The maintenance of a normal tear film depends on the maintenance of a normal ocular surface. Similarly, the ocular surface cannot retain its normal structure in the absence of a normal tear film. For these reasons, the division between the eye and the tear film is really an artificial one, and descriptions of the tear film should begin with the ocular surface.[19]

The ocular surface encompasses the entire epithelial surface of the cornea, limbus, and conjunctiva. It is physically contiguous with the adjacent eyelids and adnexa and shares important protective functional relationships with the external eye.

Under the precorneal tear film lies the anterior surface of the cornea, which is made up of nonkeratinised, stratified squamous epithelium. This highly organized epithelium has plentiful desmosomes and tight junctions, thereby providing paracellular permeability barriers to limit nonionic solutes and to maintain the homeostasis of intraocular milieu. Disruption of this physiological barrier may lead to punctate epitheliopathy and compromised wound healing.

The limbus is a unique structure that acts as a junctional barrier to separate the cornea and conjunctiva. In humans, the limbal palisades of vogt, representing specialized regions of epithelial structure, are the location of limbal stem cells. In the absence of these cells, epithelial wound healing is compromised.

Conjunctiva

Conjunctival epithelium consists of different layers. The deepest layer consists of cylindrical cells (as in epidermis), with intermediate layers of polyhedral cells. The most superficial layer is flat but indented. Goblet cells are absent at muco-cutaneous junction, begin to appear and are very numerous beyond the sub tarsal folds. From the fornix to limbus, the epithelium becomes less glandular losing its goblet cells and more epidermal in type, but never keratinized. At the limbus the epithelium is stratified and papillae form giving the deep aspect a characteristic sinuous profile.

Goblet cells are most dense, nasally, least dense in the upper temporal fornix and absent at the palpebral muco cutaneous junction and limbus. They are chief source of mucin. They arise from basal layer of epithelium and tend to retain attachment to its basement membrane. They are round to oval in shape, 10 to 20 µm wide and with flat basal nuclei. Cells become larger and more oval as they approach the surface where they develop a stoma and discharge their mucin content. Electron microscopy shows that they are attached by desmosomes to the neighbouring epithelial cells. The density of goblet cells is 10 ± 3 cells/mm^2.

Cytology

Bulbar conjunctiva is composed of stratified columnar epithelium. The cells are round, pyramidal or elongated cylindrical measuring 15 to 25 µ in diameter. Cytoplasm is semitransparent, adequate to abundant. It stains blue green with papinicolou stain. Border is well defined, sharp and regular. Some

cells may have intracytoplasmic, orange brown melanin granules. No cilia or terminal bars are present.

The nucleus is single, round to oval, eccentric, measuring 6 to 9 µm in diameter. It has smooth regular membrane and moderately course granular chromatin that is uniformly distributed. Nucleolus is single, small, red and round.

Tear film

Tear film which covers the ocular surface is a complex fluid secreted by several orbital glands and ocular surface epithelial cells. Human tears are distributed between:

- The marginal tear strip [or tear meniscus]
- The preocular film [or pre corneal film]
- The conjunctival sac.

The average tear flow in humans is about 1.2 µl/min and ranges between 0.5 and 2.2 µml/min. The volume of the tear fluid averages about 7 µl. About 1.1 µl of this total volume lies in the preocular film within the palpebral fissure, about 2.9 µl within the marginal strips, and about 4.5 µl within the fornices.[19]

The precorneal tear film

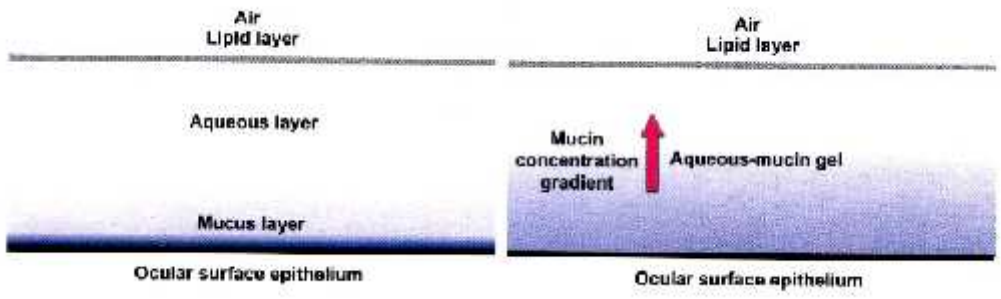


Figure 1. Traditional and modern concept of tear film.

The exact nature of tear film is controversial. Traditionally, the precorneal tear film has been thought to be tripartite, with a lipid superficial layer about 0.1 μm in thickness [with the eyelids open], an aqueous midphase 7 μm thick, and a mucin basal layer 20-50 nm thick. Although this is still the most prevalent concept, some recent evidence suggests that the tear film may be as thick as 40 μm and is largely made up of a mucin gel or partial mucin layer with an increase in mucin content basally and without discrete separation of the aqueous and mucin layers.[20]

The lipid layer

The most superficial layer of the tear film [approximately 100 molecules thick] contains polar and non polar lipids primarily secreted by meibomian [tarsal] glands located in the tarsal plate of upper and lower eyelids.

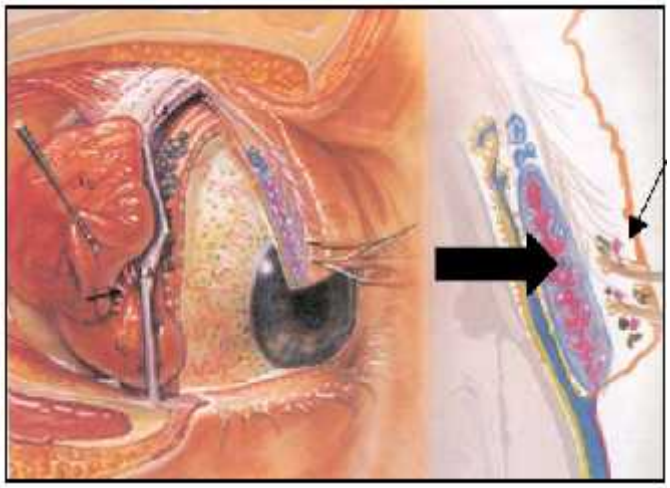


Figure 2. Glands involved with lipid secretion [Meibomian glands (thick arrow), Glands of Moll and Zeis (thin arrow)]

There are approximately 30-40 meibomian glands in the upper eyelid and 20-30 smaller glands in the lower eyelid. Each gland orifice opens onto the skin of the eyelid margin, between the tarsal gray line and the mucocutaneous junction. The sebaceous glands of Zeiss, located more anteriorly in the lid margin in relation to the lash roots, also secrete lipid which is incorporated into the tear film. The superficial oily layer is estimated to be only 0.1μm thick.[19]

Regulation of secretion

Although it is well known that blinking controls the release of meibomian gland fluid that is secreted into the duct and stored there, the stimuli that induce secretion [the rupture of alveolar cells] are less well known.

There is evidence that androgens sex steroids are the possible candidates for regulation of meibomian gland synthesis and secretion. The androgen deficiency in humans appear to be associated with meibomian gland dysfunction,

altered lipid profiles in secreted meibomian gland fluid, a decreased tear film breakup time and functional dry eye. Additional candidates for the regulation of meibomian gland secretion are the nerves that surround the acinar cells of the alveoli, mainly parasympathetic nerves, that are cholinesterase-positive and contain Vasoactive Intestinal Polypeptide [VIP]. More research into the regulation of meibomian gland secretion is needed to determine the role of harmones and nerves in the control of secretion.[21]

Secretory product

The meibomian gland fluid contains a complex mixture that may vary considerably in individuals. Typically the wax monoesters and sterol esters are the major constituents making up about 60-70% of the lipid. The minor constituents include hydrocarbons, triglycerides, diglycerides, free sterols [including cholesterol], free fatty acids and polar lipids [including phospholipids]. The mixture of lipids secreted by meibomian gland melts at 35 deg. centigrade and is thus liquid on the surface of the eye.[19]

The functions of the lipid layer are to retard evaporation, contribute to the optical properties of the tear film because of its position at the air-tear film interface, maintain a hydrophobic barrier [lipid strip] that prevents tear overflow by increasing surface tension and to prevent damage to lid margin skin by tears.[19]

The aqueous phase

The middle aqueous layer is secreted primarily by the main and accessory lacrimal glands (Figure 3)

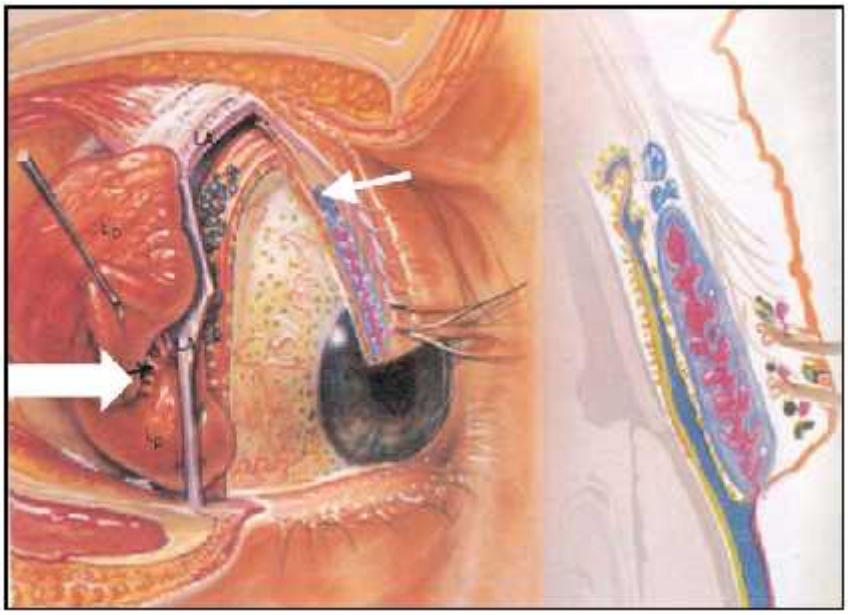


Figure 3. Glands involved with Aqueous tears secretion [Lacrimal Gland (thick arrow), Glands of Krause (thin arrow), Glands of Wolfring (thin arrow)]

The Main lacrimal gland [MLG] is the major contributor to the aqueous layer of the tear film. This gland is almond shaped and is located within the orbit on the anterior and lateral parts of the roof. The gland is highly lobular with numerous ducts that open via orifices just in front of the lateral part of the superior fornix. In humans, it is a tubuloacinar exocrine gland with 6 to 12 ducts from which lacrimal gland fluid is secreted into the ocular surface. Accessory lacrimal glands of Krause and Wolfring are minor but significant contributors to the aqueous layer of the tear film as they secrete proteins, electrolytes, and water. The glands of Krause, which constitute two thirds of the accessory lacrimal gland, lie mostly in the conjunctiva of the superotemporal fornix, with a few glands lying in the inferotemporal fornix. The glands of Wolfring are larger but fewer in number than the glands of Krause and lie in the conjunctiva

approximately at the fornicial ends of the tarsal plates. The accessory lacrimal glands are structurally like the main lacrimal gland. The cornea is also a possible source of both electrolytes and water in the aqueous layer of tears. The corneal epithelium contains Na+, K+ ATPase and is able to transport Na+, Cl-, and water into the tears. The magnitude of corneal epithelial secretion, however, is minor compared to that of the main lacrimal gland.

The conjunctiva is the final source of electrolytes and water in the aqueous layer of the tear film. As it occupies 17 times the surface area of cornea in humans, the conjunctiva most likely contributes a larger proportion to the tear film than cornea.

Regulation of secretion

Aqueous tear secretion is largely a reflex mechanism. Cranial nerve V is the afferent pathway in the reflex tear arc. Stimulation of receptors in the fifth nerve distribution in the cornea, conjunctiva, or nasal mucosa induces tear secretion from the lacrimal gland. The efferent pathway is more round about. Parasympathetic fibers leave cranial nerve VII in the greater superficial petrosal nerve and pass to the sphenopalatine ganglion. From there the lacrimal secretory nerve fibers travel with the zygomaticotemporal nerve of the maxillary division (V^2) and join the lacrimal (sensory) nerve of the ophthalmic division (V^1) of CN V before entering the lacrimal gland. Sympathetic efferent pathways may also be involved. Reduction of tear secretion and associated dry eye syndrome can be caused by diseases such as familial dysautonomia or, more commonly, by medications affecting the autonomic system.[22]

The lacrimal gland also receives hormonal input. Hormones originating from hypothalamic, pituitary gonadal axis have been shown to exert significant influence on growth, differentiation, structural profile and functional activity of the lacrimal gland.

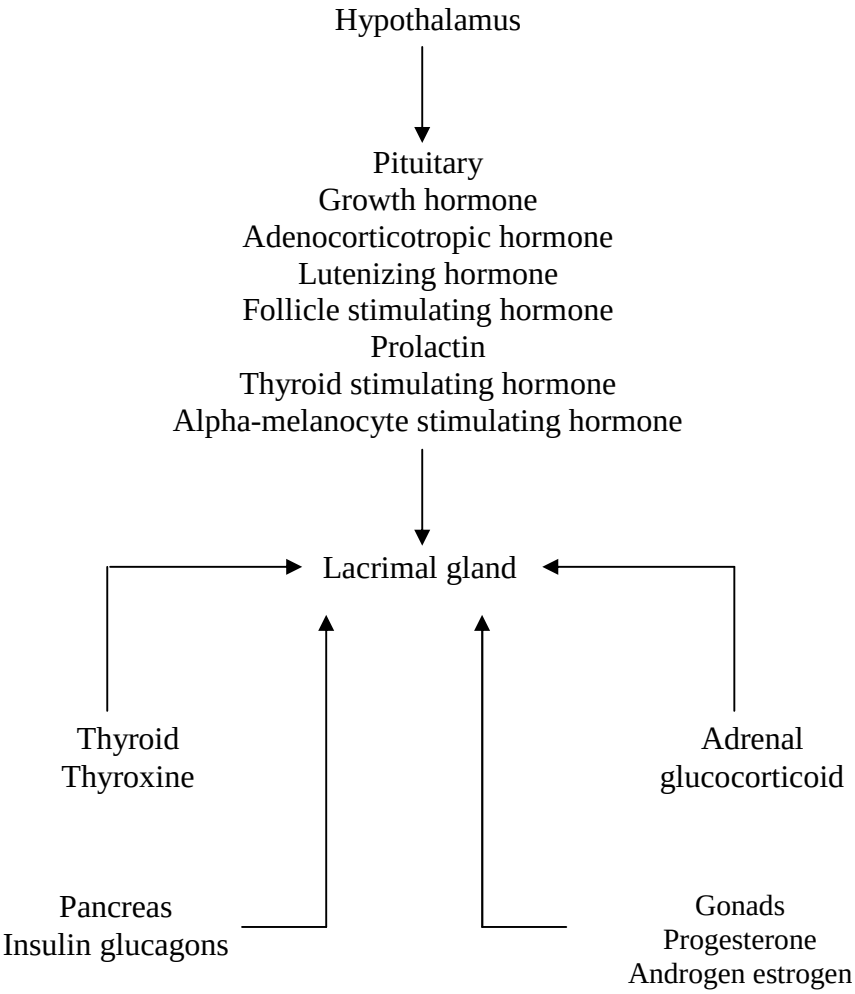


Figure 4. Schematic diagram showing the hormones known to influence the structure or function of the lacrimal gland.[21]

One of the most potent hormones that acts on the lacrimal gland is androgen. This sex steroid not only stimulates the secretion of specific proteins but appears to account for many of the morphology, biochemistry, molecular biology, immunology, and secretory out put of lacrimal tissue.

In addition to these hormones, glucocorticoids, retinoic acid, insulin, and glucagon are also known to influence the functional and secretory aspects of the lacrimal gland. The mechanism of action of all these hormones is undoubtedly mediated through an interaction with specific receptors.

Systemic medications are a common source for the inhibition of efferent lacrimal gland secretion. Numerous medications are associated with dry eye (mainly anticholinergic, antiadrenergic, thiazide and diuretics), many of which reduce lacrimation through either cholinergic inhibition of the lacrimal gland or systemic dehydration.[23]

Regulation of secretion is through sensory, sympathetic and parasympathetic nerves for both cornea and conjunctiva, composition closely resembles that of lacrimal acinar cells.[21]

Secretory Product

The aqueous layer of tears consists of electrolytes, water, proteins, and a variety of other solutes secreted by the main and accessory lacrimal glands, as well as the corneal and conjunctival epithelia. Electrolytes and small molecules regulate the osmotic flow of fluids between the corneal epithelial cells and the tear film, buffer tear pH, and serve as enzyme cofactors in controlling membrane permeability. The Na+ concentration of tears parallels that of serum; the concentration of K^+ is 5-7 times greater than that in serum. Na^+, K^+, and Cl^- regulate the osmotic flow of fluids from are enzyme cofactors from the cornea to the tear film. Bicarbonate regulates tear pH. Other tear electrolytes are Fe^{2+}, Cu^{2+}, Mg^{2+}, PO^{2-}.

The electrolyte gradients between tears and serum and between tears and aqueous humor are maintained by the blood-tear and aqueous-tear barriers, and because of this the cornea and conjunctiva normally exist in a unique electrolyte milieu.

Tear film solutes include urea, glucose, lactate, citrate, ascorbate, and amino acids. All enter the tear film via the systemic circulation, and their concentrations parallel serum levels. Fasting tear glucose levels are 3.6-4.1 mg% in diabetic and nondiabetic persons .However, after a 100 mg oral glucose load, tear glucose levels exceed 11 mg% in 96% of diabetic persons tested.

Proteins in the tear film include immunoglobulin A (IgA) and secretory IgA (S-IgA). IgA is formed by plasma cells in interstitial tissues of the main and accessory lacrimal glands and substantia propria of the conjunctiva. IgA plays a role in local host defence mechanisms of the external eye, as shown by the increased levels of IgA and IgG in human tears associated with inflammation. Other immunoglobulins in tears are IgM, IgD, and IgE. Lysozyme, lactoferrin, group II phospholipase A2, lipocalins, and defensins are important tear antimicrobials constituents. Also present in tears is interferon, which inhibits viral replication and may be efficacious in limiting the severity of ulcerative herpetic keratitis. Tears also contain a wide array of cytokines and growth factors, including tumour growth factor beta, epidermal growth factor, beta fibroblast growth factor, interleukin-1alpha and -1beta, and tumor necrosis factor alpha. These may play a role in proliferation, migration, and differentiation of corneal and conjunctival epithelial cells. They may also regulate wound healing of the ocular surface. In humans it has been shown that the concentration of lysozyme, a

bacteriolytic protein, increases with increased tear secretion and decreases with decreased tear secretion.[19]

The aqueous layer has following functions: Supply oxygen to the avascular cornea, maintain a constant electrolyte composition over the ocular surface epithelium, provide an antibacterial and antiviral defence, smoothens minute irregularities of the anterior corneal surface, wash away debris and modulate corneal and conjunctival epithelial cell function.[19]

The Mucus Layer

Tear mucins are secreted principally by the conjunctival goblet cells, the stratified squamous cells of the conjunctival and corneal epithelia, and minimally by lacrimal glands of Henle and Manz.[19]

The mucin layer of the tear film coats the microplicae of the superficial corneal epithelial cells and forms a fine network over the conjunctival surface. It contains mucins, proteins, electrolytes, and water.

Secretion of mucus layer of Tear film

Goblet cells, which are interspersed among the stratified squamous cells of the conjunctiva are one of the most important source of mucus in the mucus layer of the tear film. The stratified squamous cells of the cornea and conjunctiva also secrete mucus into tears and are discussed subsequently.

Goblet cells are distributed singly or in clusters throughout the conjunctiva. In humans, the clusters of goblet cells have been identified as mucus

crypts. Goblet cells contain the synthetic enzyme for the undirectional synthesis and secretion of mucin secretion. Mucin secretion occurs by fusion of secretory granule membranes with each other and then with the apical membrane. Once the secretion has been stimulated the entire granule contents of a goblet cell are released, a mechanism known as apocrine secretion. The goblet cell body remain to resynthesize mucus and secrete again.

Given the importance of goblet cells and the fact that various ocular surface diseases are associated with an increase or decrease in mucin levels, attempts have been made to correlate changes in the number of goblet cells with the degree of ocular abnormality. However, although such a correlation might have significant diagnostic potential, the analysis of alteration in goblet cells density has proved difficult.[21]

Regulation of secretion

Nerves appear to stimulate goblet cell mucin secretion. There is sensory (neural) stimulus to the cornea-induced goblet cell secretion via effective parasympathetic and sympathetic nerves in the conjunctiva or via antidromic stimulation of sensory nerves in the conjunctiva. The secretion is blocked by local anesthetics implicating nerves in this process. This stimulation of either parasympathetic or sympathetic nerves appears to induce goblet cell mucin secretion.

Discharge of mucus from the goblet cells also occurs when the electrolyte composition of the adjacent fluid differs from normal tear fluid, or when the osmolarity increases. This can be thought of as a protective mechanism- a

mechanism for the ocular surface to recognize foreign material and to discharge mucus to trap it and, in association with aqueous tear secretion, remove it from the eye. A second source of mucin in tears is the outer layer of cells in both conjunctiva and cornea, which contain numerous small, secretory vesicles.[21]

Mucins are heterogeneous collection of negatively charged high molecular weight glycoproteins of which carbohydrates represents a substantial proportion of the mass.[19]

Functions of the mucous layer include the following:

The mucins convert the corneal epithelium from a hydrophobic to a hydrophilic layer, which is essential for the even and spontaneous distribution of tear film. Mucins also interact with the tear lipid layer to lower surface tension, thereby stabilizing the tear film. The loose mucin network covering the bulbar conjunctiva traps exfoliated surface cells, foreign particles, and bacteria.

Goblet cell mucin production is 2-3µl/day, which contrasts with aqueous tear production of 2-3 ml/day. Tear dysfunction may result when tear mucins are deficient in number [avitaminosis A, conjunctival destruction], excessive in number [hyperthyroidism; foreign body stimulation; allergic, vernal, and giant papillary conjunctivitis], biochemically altered [keratoconjunctivitis].[19]

Role of blinking

Blinking serves to carry secreted tear fluid from the superior and inferior marginal menisci over the anterior surface of the eye, continuously reestablishing the tear film over the cornea. Also blinking action wipes debris and particulate

matter from the surface of the cornea and sclera. Goblet cells of tarsal conjunctiva release mucus which coats it's smooth surface and spread a mucin layer on the surface of corneal epithelium. Normal blink rate is 12 to 15 /min. Blinking is strongly influenced by external events, loud noise and bright flash elicits immediate blink by reflex action.

Long reading, watching a computer monitor (usually intensive task) reduces blink rate.[21]

Prevalence of dry eye

Dry eye syndrome is far more prevalent than was previously considered. Dry eye is a common condition which affects 10%-15% of adults.[8] The condition is most common among the elderly population. There is higher prevalence among women than men, with women experiencing a sharp increase in prevalence earlier than men (roughly at the age of menopause).

In a study by Sahai Anshu et al,[24] prevalence of dry eye in Indian population was 18.4%.

In a study of 3722 participants in the Beaver Dam Eye Study[11] aged from 48 to 91 years, the overall prevalence of dry eye was 14.4%**.** The prevalence varied from 8.4% in patients younger than 60 years to 19.0% in patients aged 80 years or older. The age adjusted prevalence was 11.4% for men and 16.7% for women ($p<0.001$).

In a follow up study performed 5 years later, Moss et al found that a history of dry eye developed in 322 of 2414 participants (13.3%).[25] The incidence

was significantly associated with age ($p<0.001$). After adjustment for age, the incidence was greater in patients with a history of allergy or diabetes, those who used antihistamines or diuretics, and poorer self-rated health ($p<0.05$).however, the age adjusted incidence was lower for those patients using angiotensin-converting enzyme inhibitors or who consumed alcohol ($p<0.05$).

Race: No known racial predilection exists.

Risk factors

There are significant comorbidities, associated disease, and behavioral and environmental factors that contribute to the severity of dry eye, including inflammatory and autoimmune diseases, age, diabetes mellitus, thyroid disease, sjogren's disease, corneal transplantation, previous keratitis or corneal scarring, cataract surgery, laser in situ keratomileusis, some systemic medications, contact lens wear and environmental conditions.[26]

Classification of Dry Eye

A classification system formulated by the National Eye Institute distinguishes 2 main categories (or causes) of dry eye states, tear deficiency state and an evaporative state.[18]

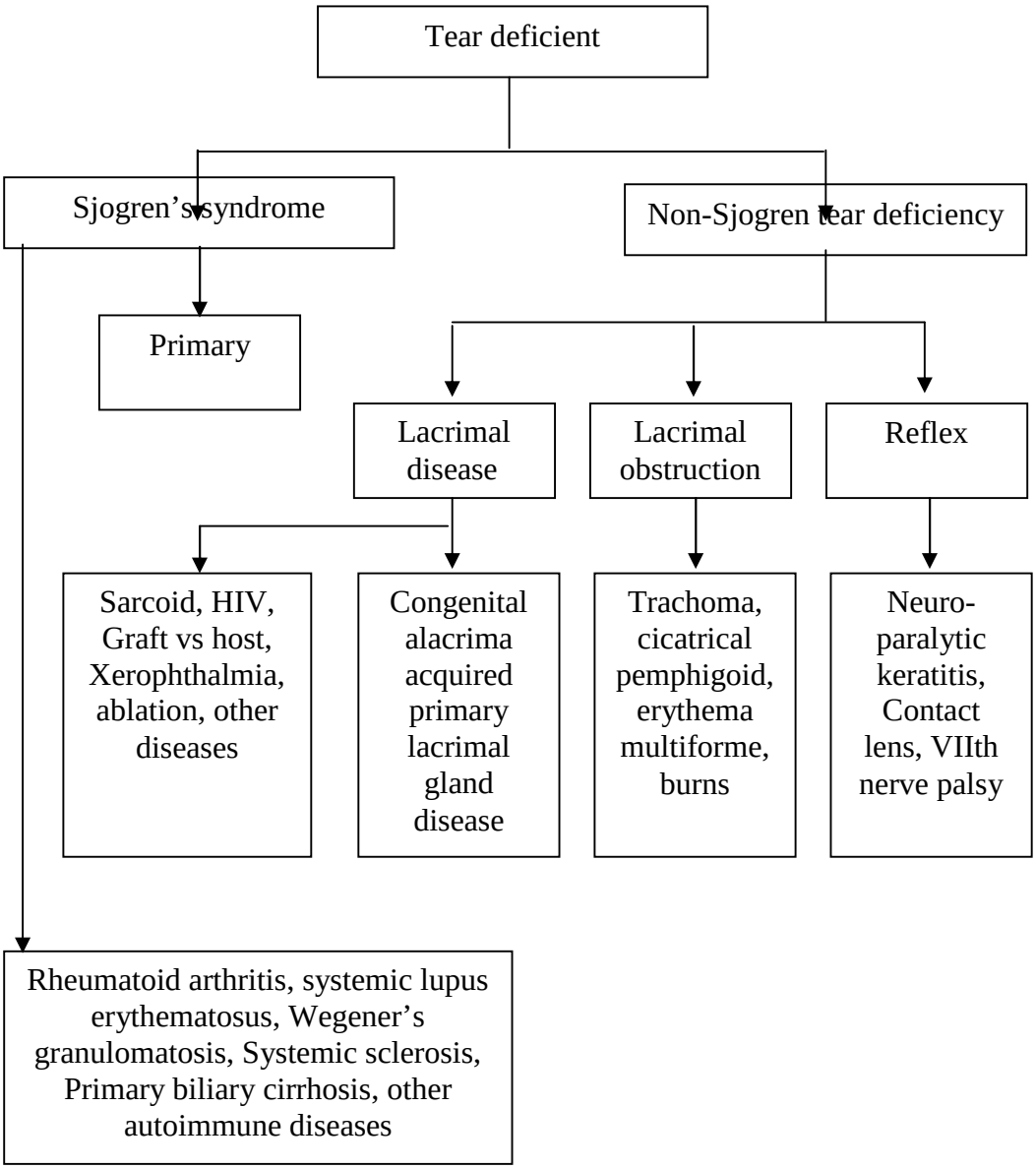


Figure 5. Tear deficiency state

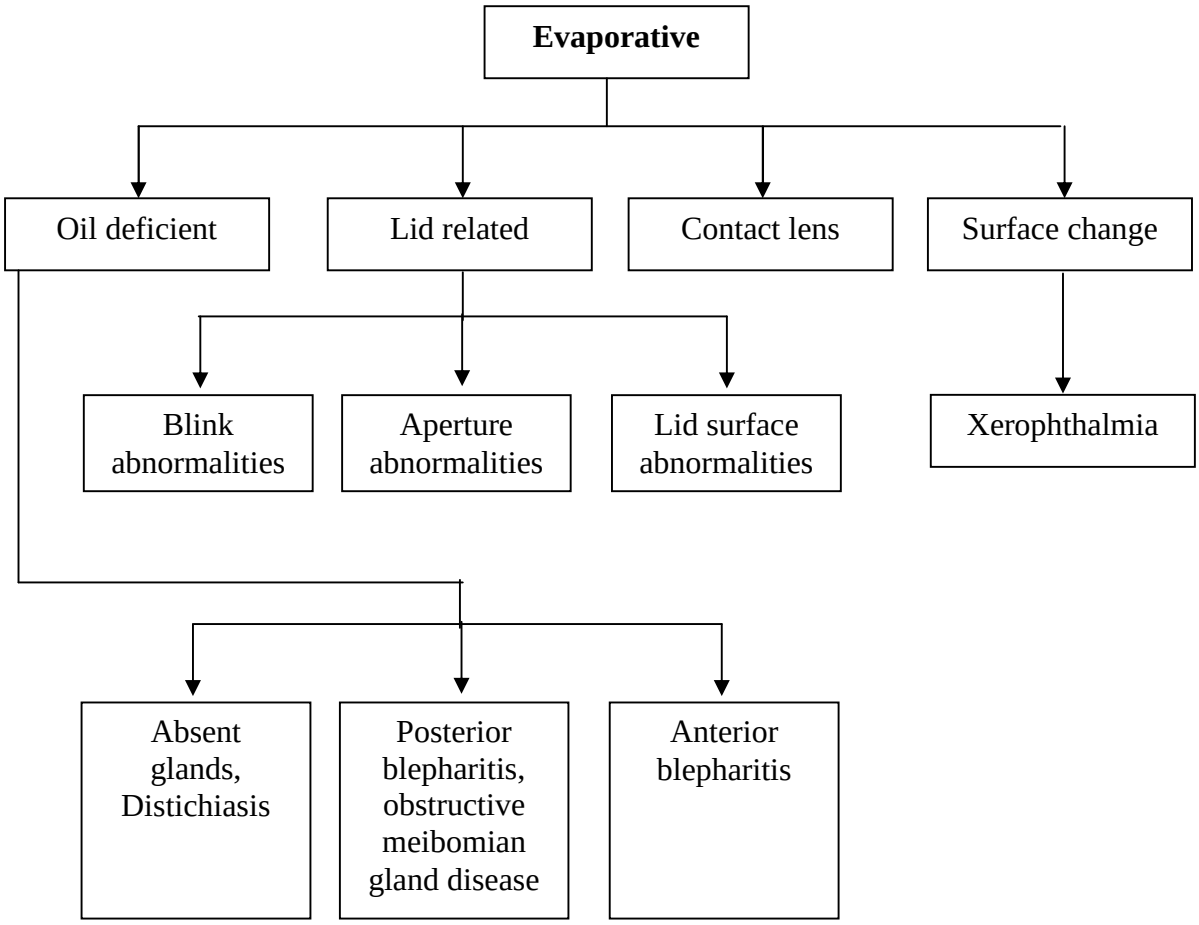


Figure 6. Evaporative state

As diabetes is one of the risk factor for the development of dry eyes.

Diabetes mellitus

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the DM, factors contributing to hyperglycemia include

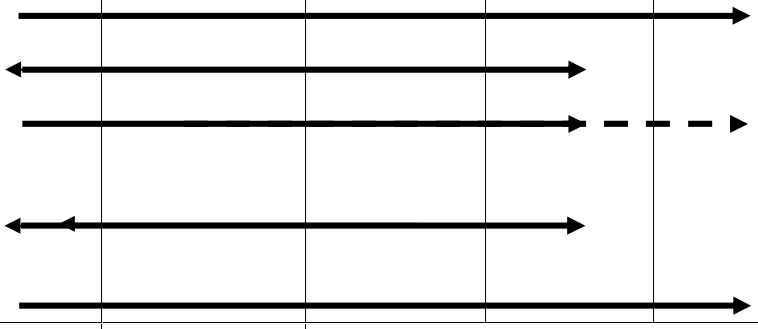
1. Reduced insulin secretion
2. Decreased glucose utilization
3. Increased glucose production.

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness.[1]

Classification

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[1] The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic process progresses. Type 1 diabetes is the result of complete or near-total insulin deficiency.

Spectrum of glucose homeostasis and diabetes mellitus[1]

Type of diabetes	Normal glucose tolerance	Hyperglycemia			
		Impaired fasting glucose or impaired glucose tolerance	Diabetes mellitus		
			No insulin required	Insulin required for control	Insulin required for survival
Type 1					
Type 2					
Other Specific types					
Gestational diabetes					
Time (years)					
FPG (mg/dl)	< 100	100-125	≥ 126		
2-h pg (mg/dl)	< 140	140 – 199	≥ 200		

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Etiologic Classification of Diabetes Mellitus[1]

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

   a. Immune-mediated

b. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes.

a. Genetic defects of β cell function characterized by mutations in:

i. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1).

ii. Glucokinase (MODY 2).

iii. HNF-1 (MODY 3).

iv. Insulin promoter factor-1 (IPF-1; MODY 4).

v. HNF-1 (MODY 5).

vi. NeuroD1 (MODY 6).

vii. Mitochondrial DNA.

viii. Subunits of ATP-sensitive potassium channel.

ix. Proinsulin or insulin conversion.

b. Genetic defects in insulin action

i. Type A insulin resistance.

ii. Leprechaunism.

iii. Rabson-Mendenhall syndrome.

iv. Lipodystrophy syndromes.

c. Diseases of the exocrine pancreas-pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase.

d. Endocrinopathies-acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

e. Drug or chemical induced-vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine.

f. Infections - Congenital rubella, cytomegalovirus, coxsackie.

g. Uncommon forms of immune-mediated diabetes "stiff-person" syndrome, anti-insulin receptor antibodies.

h. Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

Epidemiology

Diabetes is fast becoming the epidemic of the 21st century. Type 2 diabetes, which is more prevalent (more than 90% of all diabetes cases) and the main driver of the diabetes epidemic, now affects 5.9% of the world's adult population with almost 80% of the total in developing countries. Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000.[28]

World Health Organization reported that, 346 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high blood sugar. More than 80% of diabetes deaths occur in low- and middle-income countries. WHO projects that, diabetes deaths will double between 2005 and 2030. [1,28]

Race

The prevalence of type 2 diabetes mellitus varies widely among various racial and ethnic groups. Type 2 diabetes mellitus is becoming virtually pandemic in some groups of Native Americans and Hispanic people. The risk of retinopathy and nephropathy appears to be greater in blacks, Native Americans, and Hispanics.[29]

Sex

Type 2 diabetes mellitus is slightly more common in older women than men.[29]

Age

While type 2 diabetes mellitus traditionally has been thought to affect individuals older than 40 years, it is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese. In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults. Virtually all cases of diabetes mellitus in older individuals are type 2.[29]

Indian scenario

Several epidemiological studies in migrant Indians and India itself show that, the population has a high genetic predisposition for diabetes, which is precipitated by environmental factors such as urbanization.[16] The prevalence of diabetes is four to six fold lower in rural areas, which is probably attributed to a conventional lifestyle which has beneficial effect on glucose tolerance (GT). National Urban Diabetes Survey done in six cities, found age standardized prevalence rates of 12% for diabetes; with a slight male preponderance and 14% for impaired glucose tolerance. Subjects under the age of 40 years, had a prevalence of five percent for DM and 13% prevalence of impaired glucose tolerance.[1]

The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.[30] It is clear that in the last two decades, there has been a marked increase in the prevalence of diabetes among both urban as well as the rural Indians, with a suggestion that Southern India has seen the sharpest increase. Subsequent studies confirmed this high prevalence of diabetes in urban south India. Although in rural India the prevalence of diabetes is much lower than in the urban population, even here the prevalence rates are rapidly rising, though clearly more studies are needed. Variations in the prevalence rates of diabetes in different urban populations of India are expected because of the large variation in the prevalence of cardiovascular risk factors in different regions and states [85, 86]. It is evident that there is a shift in age of onset to younger age groups, which is alarming and this could have adverse effects on the nation's economy. Hence,

the early identification of at-risk individuals and appropriate intervention to increase physical activity, bring about changes in dietary habits could to a great extent help to prevent/ delay, the onset of diabetes and thus reduce the burden due to its associated complications in India.[27]

Pathophysiology

Hyperglycemia results from lack of endogenous insulin, which is either absolute, as in type 1 diabetes mellitus, or relative, as in type 2 diabetes mellitus. Relative insulin deficiency usually occurs because of resistance to the actions of insulin in muscle, fat, and the liver and an inadequate response by the pancreatic beta cell. Insulin resistance, which has been attributed to elevated levels of free fatty acids in plasma,[1] leads to decreased glucose transport in muscle, elevated hepatic glucose production, and increased breakdown of fat.

Presumably, the defects of type 2 diabetes mellitus occur when a diabetogenic lifestyle (excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed upon a susceptible genotype. The body mass index at which excess weight increases risk for diabetes varies with different racial groups. For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight.[1] A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

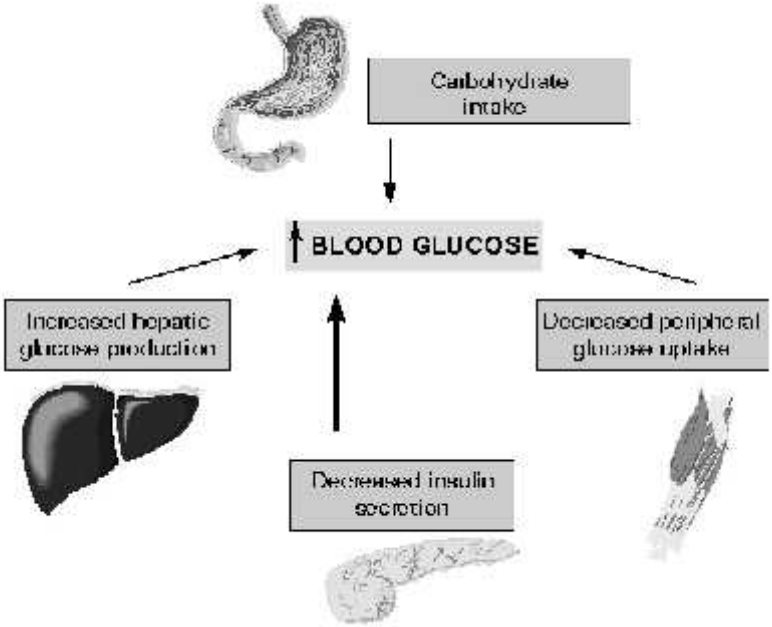


Figure 7. Pathophysiology of type 2 diabetes mellitus

Hyperglycemia appears to be the determinant of microvascular and metabolic complications. However, glycemia is much less related to macrovascular disease. Insulin resistance with concomitant lipid (ie, small dense low-density lipoprotein [LDL] particles, low high-density lipoprotein-cholesterol [HDL-C] levels, elevated triglyceride-rich remnant lipoproteins) and thrombotic (ie, elevated type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen) abnormalities, as well as conventional atherosclerotic risk factors (eg, family history, smoking, hypertension, elevated low-density lipoprotein-cholesterol [LDL-C], low HDL-C) determine cardiovascular risk.

Diagnosis

The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM based on the following premises:[1]

Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose 7.0 mmol/L (126 mg/dL)[b] *or*
- Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Risk factors for Type 2 Diabetes Mellitus

- Family history of diabetes (i.e. parent or sibling with type 2 diabetes)
- Obesity (BMI≥25 kg/m2)
- Habitual physical inactivity
- Race/ethnicity (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified IFG or IGT
- History of GDM or delivery of baby > 4kg (>9 Ib)
- Hypertension (blood pressure ≥ 140/90 mHg)
- HDL cholesterol level ≤ 35mg/dL (0.90mmol/L) and / or a triglyceride level ≥ 250mg/dL (2.82 mol/L)
- Polycystic ovary syndrome or acanthosis nigricans.
- History of vascular disease.

Complications

Diabetes has both acute and long term complications.[1] They are:

Acute

- Diabetic ketoacidosis
- Hyperglycemic Hyperosmolar state
- Hypoglycemia

Long term:

- Retinopathy
- Neuropathy
- Nephropathy
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Hypertensia.

Others

- ***Infections***
  - UTI
  - Tuberculosis
  - Candidiasis – oral / vulvovaginal
  - Mucor mycosis
  - Necrotising fasciitis
  - Periodontitis
- Dupuytrens contracture

- Pseudogout

Diabetic retinopathy

Diabetic retinopathy is a frequent cause of blindness in patients aged 20-64 years.

Epidemiology

The prevalence of all types of retinopathy in the diabetic population increases with the duration of diabetes and patient age. DR is rarely found in children younger than 10 years of age, regardless of the duration of diabetes. The risk of developing retinopathy increases after puberty.

Pathophysiology

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease.[32]

Platelets and blood viscosity

The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased RBC deformability, increased platelet aggregation, and adhesion predispose to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which in turn contributes to the development of diabetic retinopathy.

Aldose reductase and vasoproliferative factors

Fundamentally, diabetes causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic effect on retinal capillaries causing them to be both functionally and anatomically incompetent.

A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (eg, glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of its primary function (ie, autoregulation of retinal capillaries).

Loss of function of pericytes results in weakness and eventual saccular outpouching of capillary walls. These microaneurysms are the earliest detectable signs of DM retinopathy.

Ruptured microaneurysms (MA) result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages). Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates. If the swelling and exudation would happen to involve the macula, a diminution in central vision may be experienced. Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR). However, it is not exclusively seen in patients with NPDR, but it may also complicate cases of proliferative diabetic retinopathy (PDR).

Another theory to explain the development of macular edema deals with the increased levels of diacylglycerol (DAG) from the shunting of excess glucose. This is thought to activate protein kinase C (PKC), which, in turn, affects retinal blood dynamics especially permeability and flow leading to the fluid leakage and retinal thickening.

As the disease progresses, eventual closure of retinal capillaries occurs, leading to hypoxia. Infarction of the nerve fiber layer leads to the formation of cotton-wool spots (CWS) with associated stasis in axoplasmic flow.

More extensive retinal hypoxia triggers compensatory mechanisms within the eye to provide enough oxygen to tissues. Venous caliber abnormalities, such as venous beading, loops, and dilation, signify increasing hypoxia and almost always are seen bordering the areas of capillary nonperfusion. Intraretinal microvascular abnormalities (IRMA) represent either new vessel growth or remodeling of preexisting vessels through endothelial cell proliferation within the retinal tissues to act as shunts through areas of nonperfusion.

Further increase in retinal ischemia triggers the production of vasoproliferative factors that stimulate new vessel formation. The extracellular matrix is broken down first by proteases, and new vessels arising mainly from the retinal venules penetrate the internal limiting membrane and form capillary networks between the inner surface of the retina and the posterior hyaloid face.

Neovascularization most commonly is observed at the borders of perfused and nonperfused retina and most commonly occur along the vascular arcades and at the optic nerve head. The new vessels break through and grow along the

surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise. However, they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.

These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the degree of fibrous tissue formation. In later stages, the vessels may regress leaving only networks of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections. Traction may cause retinal edema and both tractional retinal detachments and retinal tear formation with subsequent detachment.[32]

Classification of retinopathy

Early treatment diabetic retinopathy study[33] (ETDRS) has classified retinopathy as follows.

Non Proliferative Diabetic Retinopathy (NPDR)

- Mild nonproliferative diabetic retinopathy
    - Presence of at least 1 microaneurysm or intra retinal haemorrhage.
    - Hard or soft exudates may or may not be present.
- Moderate nonproliferative diabetic retinopathy.

  - Presence of microaneurysms or intra retinal haemorrhages into two or three quadrants.
  - Early mild IRMA.
  - Hard or soft exudates may or may not be present.
- Severe nonproliferative diabetic retinopathy (4-2-1) any one of the following.
  - Hemorrhages and microaneurysms in 4 quadrants
  - Venous beading in at least 2 quadrants
  - IRMA in at least 1 quadrant
- Very severe nonproliferative diabetic retinopathy (4-2-1) any two of the following.
  - Hemorrhages and microaneurysms in 4 quadrants
  - Venous beading in at least 2 quadrants
  - IRMA in at least 1 quadrant
- Early proliferative diabetic retinopathy - Presence of new vessels but not meeting the criteria for high-risk PDR
- High-risk proliferative diabetic retinopathy
  - NVD one fourth to one third of disc area with or without vitreous haemorrhage or pre retinal haemorrhage
  - NVD less than one fourth disc are with vitreous haemorrhage or preretinal hemorrhage
  - NVE greater than or equal to one-half Disc area with preretinal or vitreous hemorrhage.

Maculopathy

The terms ‘diffuse’, ‘exudative’ and ischaemic diabetic maculopathy’ were not employed in the Early treatment of Diabetic Retinopathy Study (ETDRS). Instead, patients were given macular focal laser therapy based on Clinically significant macular oedema was present or not. This is defined as.

1. Retinal thickening at or within 500μ (One third of the diameter of the optic disc) at the center of the macula.
2. Hard exudates at or within 500μ at the center of the macula, if there is thickening of the adjacent retina.
3. An area of retinal thickening greater than one optic disc area in size at lest a part of which is within one disc diameter of the center of the macula.

Advanced diabetic eye disease

End result of uncontrolled proliferative diabetic retinopathy marked by complications such as;

- Persistent vitreous haemorrhage
- Tractional retinal detachment
- Neovascular glaucoma

Risk factors

Duration of diabetes, glycemic control, renal disease, hypertension, elevated serum lipids and pregnancy.

Work up

Funduscopy and Fundus Fluorescein Angiography.

Medical Care:

Glucose control: The Diabetic Complications Control Trial[21] (DCCT) has found that intensive glucose control in patients with IDDM has decreased the incidence and progression of diabetic retinopathy. Although no similar clinical trials for NIDDM exist, it may be logical to assume that the same principles also apply. In fact, the American Diabetes Association has suggested that all diabetics, type I and type II should strive to maintain glycosylated hemoglobin levels of less than 7% to prevent or at the very least minimize long-term complications of DM including DM retinopathy.

Surgical Care

The advent of laser photocoagulation in the 1960s and early 1970s provided a noninvasive treatment modality that has a relatively low complication rate and a significant degree of success. This involves directing a high-focused beam of light energy to create a coagulative response in the target tissue. In NPDR, laser treatment is indicated in the treatment of clinically significant macular edema[34] (CSME) The strategy for treating macular edema depends on the type and extent of vessel leakage. If the edema is due to leakage of specific microaneurysms, the leaking vessels are treated directly with focal laser photocoagulation. In cases where the foci of leakage are nonspecific, a grid pattern of laser burns is applied.

Panretinal photocoagulation (PRP) is the preferred form of treatment for PDR. This involves applying laser (xenon arc and argon) burns over the entire retina sparing the central macular area. This may be performed using a variety of delivery systems including the slit lamp, indirect ophthalmoscope, and endoprobe. The exact mechanism by which PRP works is not entirely understood. One theory is that destroying hypoxic retina presumably decreases the production of vasoproliferative factors such as VEGF, which in turn reduces the rate of neovascularization. Another theory is that PRP allows increased diffusion of oxygen from the choroid, supplementing retinal circulation. The enhanced oxygen delivery also down regulates vasoproliferative factor production and subsequent neovascularization.[32]

Vitrectomy may be necessary in cases of long-standing vitreous hemorrhage (where visualization of the status of the posterior pole is too difficult), tractional retinal detachment, and combined tractional and rhegmatogenous retinal detachment. More uncommon indications include epiretinal membrane formation and macular dragging.

The purpose of surgery is to remove the blood to permit evaluation and possible treatment of the posterior pole, to release tractional forces that pull on the retina, to repair a retinal detachment, and to remove the scaffolding where the neovascular complexes may grow into. Laser photocoagulation through indirect delivery systems or through the erndoprobe can be performed as an adjunctive procedure during surgery to initiate or continue laser treatment.[32]

Prognosis

The ETDRS has found that laser surgery for macular edema reduces the incidence of moderate visual loss (doubling of visual angle or roughly a 2-line visual loss) from 30% to 15% over a 3-year period.

The Diabetic Retinopathy Study[35] (DRS) has found that adequate scatter PRP reduces the risk of severe visual loss (<5/200) by more than 50%.

Corneal complications

Corneal sensitivity is decreased in proportion to both the duration of the disease and the severity of the retinopathy. Corneal abrasions are common in people with diabetes, presumably because adhesion between the basement membrane of the corneal epithelium and corneal stroma is not as firm as that found in normal corneas. Hyperglycemia and the aldose reductase pathway probably play a major role in epithelial abnormalities, because aldose reductase inhibitors may accelerate healing of corneal abrasions.[32]

Dry eyes in diabetes

Epidemiology

The study of ocular surface manifestations during the course of diabetes mellitus has increased in recent years. Reported prevalence of dry eye in diabetics is diverse.

For example, 47%–67% of diabetic patients have primary corneal lesions during their lifetime.[36] In a case control study, the incidence of

keratoepitheliopathy in diabetics was found to be 22.8% compared with 8.5% in non diabetic patients. Qualitatively, abnormalities in tear secretion seems relevant to the development of diabetic keratoepitheliopathy such as superficial punctuate keratitis, recurrent corneal erosions and persistent epithelial defects.[37]

Seifart et al[38] demonstrated, in their case control retrospective study, that 57% and 70% had proven dry eye syndrome among patients with type 1 and type 2 diabetes, respectively.

Moss et al[39] however reported dry eye incidence of only18.1% in diabetic and 14.1% in non diabetic patients. The higher percentage found by Seifart and associates may reflect a selection bias in their study, resulting from selection of the more severe, hospital-treated diabetic patients compared to the community-based study by moss et al. In an earlier study by Binder et al[40] of an unselected group of type 1 diabetic patients, 55% of the patients showed signs of dry eyes some of the time. The high rate of antinuclear antibodies in this study suggested the symptoms might have an immunological basis.

In the Beaver Dam Eye Study,[41] a population-based study of individuals 43–86 years of age, patients with type 2 diabetes were more likely to respond affirmatively (19.8%) to the question, "For the past 3 months or longer, have you had 'dry eyes' (foreign body sensation with itching and burning, sandy feeling, not related to allergy)?" than those without diabetes (13.9%, P = 0.04). The difference between people with diabetes (21.3%) and with out(10.8%) was most pronounced in those in the youngest age-groups (65 years of age) and was no longer significantly different after 65 years of age.

Pathogenesis

It is still not clear why diabetic patients develop dry eyes more often than healthy subjects. One possible explanation could be an exocrine dysfunction of the main lacrimal gland in patients with diabetes mellitus or perhaps the development of additional unknown proteins in the tear fluids.[42]

Tear deficient dry eye can result from either interruption of the tearing reflex pathways or from any process that affects the ability of the lacrimal gland to secrete. The influence of insulin on the secretory immune system (immunoglobulin IgA, IgG) in patients with diabetic retinopathy(DRP) and dry eyes was described by Sullivan and Hann[43] in 1989 and clinical observations were reported by Seifart and Strempel[38] in 1994. The decrease in sensitivity of the cornea in DRP was reported by Downie and Newell[44] in 1961 and likewise by Rogell[45] in 1979 who also observed a reduction in sensitivity after laser coagulation. The diminished sensitivity may be a kind of diabetic neuropathy. This can lead to the reduction of stimulatory signals from the ocular surface to the lacrimal gland and the influence on regulatory systems. Many studies have confirmed decreased schirmer readings in diabetics compared with normal individuals.

Both total tear secretion and reflex tear secretion, but not basal tear secretion, are reduced in the diabetic patients. The decrease in total tear secretion thus appeared largely due to the decrease in reflex tear secretion. Reflex tear secretion is regulated by three stimulatory systems: the peripheral sensory system, the retinal (light) stimulation system, and the psychogenic system. Given

that corneal sensation was decreased in diabetic patients, the reduced tear secretion in these individuals might have been due to reduced stimulation from the corneal surface. However, whereas corneal sensation correlated with the stage of diabetic retinopathy, total or reflex tear secretion did not.[46]

It is possible that damage to the microvasculature of the lacrimal gland together with autonomic neuropathy may contribute to impaired function of the gland. Moreover, the various medication consumed by diabetic patients may exacerbate the dry eye state.[47]

Significant difference in the tear protein patterns of patients suffering from dry eye, diabetic patients suffering from dry eye, and healthy volunteers have been demonstrated. In one study the electrophoretic patterns from tear proteins of non-diabetic and diabetic patients were analyzed and compared to controls. The main protein peaks, lactoferrin, lysozyme, lipocalin, and albumin were detected and quantified. The number of peaks were significantly increased in the tear protein pattern of diabetics. Thus, this must be due to changes in tear protein patterns, e.g. the development of new protein peaks, not only by slight differences between the concentrations of the main protein peaks. The most important differences in protein patterns were found in the molecular weight range of 30–50 kDa. However, an increase of peaks in that molecular weight range was highly specific. Those "new" proteins, which do not exist in healthy subjects, could play a role in the pathogenesis of the diabetic disease and/or the development of eye-related complications of the diabetic disease. This study could also demonstrate that changes in protein patterns were strongly correlated with the duration of the diabetic disease. The longer the disease duration, the

more changes were expressed. The differences found might not be caused by the diabetes itself, but by the trophic or autonomic disturbances common to that condition.[48]

Some authors believe that the diabetic metabolism and perhaps tearfilm–pH value is responsible for the secretory regulation of the tear film.[49]

Aldose reductase, the first enzyme of the sorbitol pathway, may also be involved. The oral administration of aldose reductase inhibitors has been shown to improve the tear dynamics significantly.[50]

Impression cytology of the conjunctival surface showed distinctly more frequent and more pronounced signs of conjunctival metaplasia in diabetics. Several reasons could be responsible for this finding: (1) Even though the "basic" unstimulated tear flow is normal in diabetics, the decrease in reflex tearing could be sufficient to induce chronic damage of the conjunctival surface, resulting in conjunctival metaplasia. (2) The trophic function of the tear film (vitamin A, vitamin A carrier, epithelial growth factors, etc) could be disturbed in diabetics, leading to chronic trophic damage of the conjunctival surface. (3) The ocular surface changes found in diabetics could at least partially be the result of a primary surface disease or of metabolic alterations of the conjunctival epithelial cells independent of tear film abnormalities.[51]

Oxidative stress and free radical production are elevated in diabetes mellitus. Most studies have found that people with diabetes mellitus have circulating ascorbic acid concentrations at least 30% lower than people without diabetes mellitus. Human tears are rich in vitamin C which acts protectively for

the ocular tissues. Moreover, ocular tissues probably have a higher free radical activity than any other organ, mainly because of ultraviolet exposure. Higher levels of NO were found in the aqueous humour of diabetic patients and this may induce inflammatory reactions that cause cell damage.[52] Biswas et al have reported that in the resting state the level of NO were higher in diabetics compared to normal polymorphonuclear leucocytes. Macrophages have been shown to increase NO production in diabetes. The reaction of nitric oxide with superoxide (O_2^-) leads to the formation of peroxynitrite, a potent oxidant which contributes to ocular inflammation.[53]

In diabetic patients suffering from KCS, poorer glycemic control (higher mean annual HbA1c levels) led to a higher annual consumption of ocular lubrication, regardless of age.[54]

Similarly, Nepp et al[55] showed that the severity of KCS correlated with the severity of diabetic retinopathy, which is well known to correlate with glycemic control. In contrast, Binder and associates[40] reported that sicca symptoms affected some type 1 diabetic patients only during the hyperglycemic phases. This could result from high extracellular fluid osmolarity disturbing tear production, rather than representing a chronic complication of diabetes. A few studies have found no significant correlation between retinopathy and dry eyes.[46]

However the precise role of these abnormalities, individually or in combination, in the pathogenesis of dry eyes is not well defined.

Assessment of dry eye symptoms

Symptoms form an important part of assessment of any disease process and dry eye is no exception. Surveys on population based prevalence of dry eye have shown that symptoms are present in 25-35% of people.[56] However, studies have also shown a poor association between the signs and symptoms of dry eye.[57] The most common symptoms in patients of dry eye are, ocular fatigue, discomfort, grittiness, soreness, redness, foreign body sensation, light sensitivity, blurring of vision. These symptoms are found to occur in increased intensity as the day progresses.[58-60]

The National eye institute workshop on clinical trials in dry eye which gave a formal definition of dry eye concluded that all clinical trials concerning dry eye should include an assessment of subjective symptoms and functional life style through the use of a well designed and validated questionnaire and that such an instrument may be the best measure for determining the clinical efficacy of therapeutic interventions.

Numerous studies have been done to find the most common symptoms and to formulate a valid questionnaire.

The National Eye Institute visual function questionnaire (NEI VFQ - 25) is one such questionnaire to assess the symptoms of ocular disease. However, it surveys the general ocular health and is not reliable to capture the broad range of symptoms unique to a certain ocular disorder.[61]

McMonnies questionnaire, which is the patient perspective instrument specific for dry eye disease, has a formulated grading system and some published psychometric properties. It primarily uses dichotomous responses (yes or no) to assess the presence of symptoms.[62] However, it was evaluated as a screening test to discriminate subjects with dry eye from normal population and not as an instrument to grade either dry eye symptom severity or its effect on vision related function.

A self administered dry eye questionnaire (DEQ) was tested on a sample of 1054 patients in Ohio, USA. The frequency of individual symptoms were tested in contact lens and non contact lens wearers which found that nearly 47% of the patients diagnosed with dry eye had symptoms so severe that they had to stop their daily activities and close their eye more than once a week.[63]

However, none of these studies had assessed the severity of symptoms of dry eye but tested only if symptoms were present or absent. In order to overcome this drawback, the OSDI questionnaire was designed.

The ocular surface disease index questionnaire (OSDI), is a 12 item questionnaire designed to provide a rapid assessment of symptoms of ocular irritation consistent with dry eye disease and their impact on vision related functioning. The questions were generated based on patient's comments from several years of clinical studies. Each symptom is given an individual score and the final calculation takes into account the number of questions answered and the cumulative score.

Signs of dry eye

The physical findings which may be seen are- filaments, meniscus floaters, mucus strands & papillary conjunctivitis.

1. Filaments: When the cornea dries to a point that is incompatible with a healthy epithelial layer, some surface cells become dessicated and are shed, creating a small pit on the corneal surface. Lipid containing mucin will become attached to these pits; surface epithelium grows on these mucus cores and filament is formed.

2. Meniscus floaters: Arise from dead epithelial cells and fibrils of lipid contaminated mucin.

3. Mucus strands: These are strings of lipid contaminated mucus that have rolled up and been pushed into the cul de sac by shearing action of lids. These are more common in mucin deficient dry eyes.

At the cellular level: Morphological changes occur in the epithelial cells. There may be cohesion of cells, nucleo cytoplasmic ratios differ and keratinisation occurs. The changes occurring are graded based on the staining characteristics, shape of the cells, size of the nuclei and presence or absence of goblet cells.[64]

Grade 0: Epithelial cells are small and round. Nucleus is large, basophilic: N: C ratio is 1:2. Goblet cells are abundant, plump and oval. PAS positive cytoplasm is present.

Grade 1: Epithelial cells are larger and more polygonal. Eosinophilic staining cytoplasm is present. Nuclei are smaller with N: C ratio being 1 :3.Goblet cells are decreased in number but maintain their shape with intensely PAS positive cytoplasm.

Grade 2: Epithelial cells are large, polygonal, may be multinucleated. They have variably staining cytoplasm. Nuclei are small with N:C ratio of 1:4 to 1:5. Goblet cells are markedly decreased in number, smaller and less intensely positive. They have poorly defined cellular borders.

Grade 3: Epithelial cells are large, polygonal with basophilic staining cytoplasm. Nuclei are small, pyknotic or completely absent. N:C ratio is 1:6. Goblet cells are completely absent.

Psychological effects of dry eye

Dry eye syndrome is not a common cause of vision loss, but it is still a serious issue for people who have it. The symptoms become progressively troublesome and exert an increasing burden on the patients as the disease progresses or increases in severity. These types of patients have various degrees of health-related QoL impairment, can become frustrated with their treatment course, repeatedly visit doctors and specialists seeking treatment changes, and may seek alternative treatments leading to significant utilization of medical resources. Studies have shown that these patients are reported to have significant loss of productivity each year, often losing approximately 5 work days and working an average of 208 days with dry eye symptoms.[65]

It reduces the functional visual acuity of the patient and also leads to his life long dependence on his doctor. Sufferers of dry eye syndrome are more likely to report problems with daily activities, including reading, using a computer, driving and watching television, than people without dry eye syndrome.

The signs do not manifest till late stages of the disease. If not detected early, dry eye can lead to complications which are as follows:

Complications[66]

1. Sterile stromal ulcers: The corneal melt which occurs is typically an oval, non infiltrated ulcer situated at or just below the visual axis with its longest dimension horizontally. The ulcers tend to progress quickly and often perforate.
2. Blepharitis and Conjunctivitis: There is increased incidence of infection due to loss of normal antibacterial tear substances, lysozyme, 13 beta lactamase and lactoferrin.
3. Band keratopathy.
4. Keratinization.
5. Corneal vascularisation.

Tear film evaluation

Diagnostic tests

As the symptoms are nonspecific and signs do not manifest till late stages of the disease, objective assessment in the form of tests is of utmost importance in the evaluation of a suspected case of dry eye or in the screening for dry eye. There are many suggested dry eye diagnostic test batteries in literature. But, there has been no systematic description of the standard of care in diagnosing dry eye. In a retrospective review of patients charts performed in four clinical settings with a sample size of 467 patients in USA, it was found that fluorescent staining was used maximally, followed by TBUT, tear meniscus, Schirmer and Rose bengal tests. It was also found that performance of two test procedures appeared to represent the current standard care in diagnosis of dry eye.[67]

Another study conducted in Massachusets showed that the most frequent first choice test preferred by Ophthalmologists was Schirmer test and its modifications (79%) followed by rose bengal staining(59%), TBUT (47%) and fluorescent staining(50%). Tear film evaporation, tear protein analysis, tear feming and - impression cytology were found to be the least used tests for diagnosis.[68]

The global workshop on clinical trials for dry eye suggests that diagnostic tests should include those which assess the interpalpebral surface damage, tear instability and tear hyperosmolarity. Among all the tests available, 4 tests given below assess precisely these criteriae. In addition, they are easy to perform on out patient basis and harmless to the patient.

Schirmer test

This has been, for years, the most common means of measurement of tear production. The details of this test were first published in 1903. It involves folding sterile filter paper strips and inserting them between the lower lid and the globe at lateral one third of lid margin. The test can be performed with or without topical anaesthesia or with nasal stimulation.

Much confusion and disagreement exists in literature as to the validity and usefulness of Schirmer test. Without anaesthesia the test is believed to measure reflex basic tear secretion whereas with anaesthesia, tear secretion devoid of reflex components. The false positive results appear to be reduced some what if the test is performed without local anaesthesia. Studies conducted in Philadelphia have posed a question mark over the existence of an entity called pure basic secretion and the validity of performing the test with anaesthesia because the use of anaesthesia reduces conjunctival, corneal and lid margin sensitivity but does not totally suppress reflex tearing.

The Schirmer test (ST) is most commonly performed with the patient's eyes open and blinking normally, but some clinicians prefer performing it with the patient keeping his eyes closed. A study was done in Turkey, to compare the repeatability of the 2 STs. They found that, closing the eyes during ST results in less blinking and may help to maintain more stable and uniform conditions under which the test is performed, When the eyes are closed, role of the lid margins and eyelashes in stimulating tear secretion and the influence of external factors such as temperature, evaporation, and humidity are reduced. It is also easier for the

patient to keep the eyes still because external visual stimulants are absent, and this reduction in eye movements minimizes irritation caused by the paper. This in turn reduces excess reflex tearing, which is a major factor that compromises ST1s reliability. There were statistically significantly significant higher readings with the eyes open, in this study supporting this increase in reflex tearing when the eyes are open during ST.[69]

Despite conflicting reports, Schirmers test still continues to be a widely used test for assessment of dry eye.

Tear film Break Up Time (TBUT)

TBUT was described by Norn and revised by Lemp and Holly.41 It is a test which measures the tear film stability. The tears are stained with fluorescein dye and the time interval is measured between a complete blink and first appearance of a dry spot in the precorneal tear film. BUT can be measured invasively by using fluorescein (FBUT) or non-invasively using a keratometer or a xeroscope (NITBUT).

The steps involved in the break up of tear film as per Holly's (also known as Holly and Lemp's) mechaisms are as follows:

- The tear film thins uniformly by evaporation.
- When it is thinned out to some critical thickness, a significant number of lipid molecules begin to be attracted by the mucin layer and migrate down to this layer. This migration process is enhanced if there is any spontaneous local thinning.

- When the mucin layer on the endothelium is sufficiently contaminated by the lipid migrating down from the top surface of the tear film, the mucin becomes 'hydrophobic and the tear film ruptures.

Blinking then occurs to repair the rupture by removing the lipid contaminant from the mucin layer and restoring a thick aqueous layer.

The fluorescein tear break up time has been shown to be dependent on the reduction of surface tension by mucins. When the tear mucin is reduced, as reflected by a fall in conjunctival goblet cell density or arise in surface tension, BUT is also reduced.

A study was done in 1983 in Aligarh to know the BUT in normal Indian subjects, as no major study had been undertaken before this in our part of the world. It was found that BUT was lower, less than 15 seconds when compared to westerners in whom it has been found to be 20 to 30 seconds normally. The lower rate was attributed to tropical climate conditions.[70]

Another study was done in Canada in 2005, where the tear break up dynamics were videotaped in order to study the phenomenon of tear break up in dry eye and control subjects and its impact on dry eye symptoms. This study clearly demonstrated that the tear break up is more rapid and extensive among dry eye subjects compared with controls. Even after the first break, tear film of many dry eye subjects continued to disrupt over larger areas of cornea. This study has further reinforced the need for using TBUT for evaluation of dry eye.[71]

While performing the procedure, it is a common clinical practice to take several tear breakup time measurements and average the results. Nichols KK and co workers found that averaging the two readings resulted in improved repeatability.

Therefore, taking two measurements and averaging yields a longer and more repeatable tear break-up time and may be a more appropriate technique for clinical practice and clinical studies.

Rose Bengal staining

Rose Bengal is a vital dye that stains altered corneal and conjunctival epithelium. Rose Bengal staining ensues whenever there is poor protection of surface epithelium by the pre ocular tear film. In addition, it has a photo toxic effect which causes ocular irritation after instillation.[72]

The precise change in the epithelial cell membrane that permits dye uptake is still unknown. As early as 1933 Sjogren used the rose bengal stain for the diagnosis of kerato conjunctivitis sicca (KCS). Rose Bengal is a fluorescein derivative, i.e. tetrachloro tetraiodo fluorescein sodium. Despite their clinical similarity, the two dyes differ completely with regard to their staining properties. Fluorecein does not stain cells or tissues but diffuses into the intercellular spaces from a surface defect. Rose Bengal on the other hand, has the characteristic to stain surface cells of the cornea and conjunctiva that tend to keratinize.

Van Bijsterveld (1969) introduced numerical scoring for the intensity of staining with Rose Bengal of both medial and lateral bulbar conjunctiva arid of

the cornea.[73] Each section was given a score of up to three points, so that a maximum score of nine could be obtained. He found the best staining intensity score limit to differentiate between normal persons and patients with keratoconjunctivitis sicca to be 4. In his comparative study, Van Bijsterveld found that, with a score limit of 4, the combination of results of the Schirmer test and rose bengal test was no better than the results of rose bengal test alone. At the stated limit, he found the probability of misclassification to be around 5%.

It has been recommended as one of the tests which can assess ocular surface damage in dry eye.

Conjunctival Impression Cytology

Believed to be one of the best methods for study of conjunctival or ocular surface, conjunctival impression cytology by means of cellulose acetate strips was first introduced by Egbert and associates in 1977 as a minimally invasive conjunctival biopsy.[74]

It refers to the application of a cellulose acetate filter to the ocular surface to remove the superficial layers of ocular surface epithelium. These cells are then to be subjected to histological, immunohistological or molecular analysis. Generally, 2 to 3 layers of cells are removed in one application but deeper cells can be accessed by repeat application over the same site. It is non invasive, relatively easy to perform and yields reliable information about the area to be sampled.[75]

Before the introduction of this method, study of conjunctival surface was attempted using excised pieces of tissue or by scraping the conjunctival epithelium. They experimented with a variety of methods including cellophane tape, photographic film, various synthetic filters and found that onginal Millipore filters were best for this purpose. It was introduced mainly to study the goblet cell density of the ocular surface in the initial period after introduction.

In the later years, the method gained popularity and became a standard method for study of ocular surface in various conditions such as viral keratoconjunctivitis, keratoconjunctivitis sicca, vitamin A deficiency (where it can pick up mild xerophthalmia),[76] changes occurring in conjunctival epithelium in chronic renal failure (where the conjunctival epithelial features in chronic renal failure patients with or without calcium deposits have been studied),[77] surface changes which may occur in psoriasis,[78] ocular surface malignancies etc.

However, the widest application of this investigation has been in the field of dry eye syndrome. As early as 1991, Reddy M and associates did a comparative study of conjunctival biopsy versus impression cytology to study the histopathological changes occurring in conjunctiva in dry eye states and found that impression cytology was as effective as biopsy for diagnostic purposes. It helps establish not only if dry eye is present or not but also aids in grading the severity of dry eye.

Using this technique, studies have been done, not only in the field of detection of the disease process but also in looking for reversal of changes which may occur after use of topical medication.

The process has undergone tremendous improvement since the time it was introduced. Initially, the extent of modification was limited to the variation of chemicals used for processing the strips. But, in the later years, a transfer technique was introduced where the cellulose acetate impression was directly transferred to the slide which eliminated the need for processing of strips. A study done in Mumbai found that the technique was extremely useful to visualize the state of superficial conjunctival cells, is easy to perform and the time taken for the entire procedure from taking impression to seeing the slide does not take more than 8-10 minutes. The relationship of various cells to each other is also maintained.[79] A recent study has shown that nylon paper can also be used as an alternative to cellulose acetate filter paper for conjunctival impression cytology, with comparable results.[80]

A number of recent advances have improved the ability to measure dry eye clinical signs and symptoms. Standard grading scales have been developed with which ocular surface stains are assessed in various conditions. Tear film instability can be dynamically monitored through image analysis of fluorescein videography, corneal topography, interferometric imaging and optical coherence tomography, and wave front technology, which allows real-time tracking of vision during periods of tear instability.

Corneal Residence Time Test or the Tear Clearance Rate (TCR)

Several methods can be used to measure the time that pre-ocular tear film and topical eye drops remain resident on the cornea. In patients who have a normal lacrimal drainage system but abnormalities in tear production, the decay

time of an indicator such as flourescein or a radioisotope can be accurately measure. In patients with dry-eye syndrome, the residence time of flourescein or a radioisotope is prolonged because of a decrease in the turnover of tears. The flourescein concentration can be detected by clinical observation or, more accurately, by flourophotometry, the radioisotope can be measured by gamma camera. These procedures remain research tools, but may be used in certain patients with dry-eye syndrome. Other methods also are helpful in measuring the residence time of certain drugs.[81]

Tear composition assay

Tear Film Osmolarity Test

For this test, tear samples are collected with hand-drawn micropipette from the inferior marginal tear strip without disturbing the ocular surface, and tear osmolarity is determined by a freezing point depression osmometer. Normal tear film osmolarity is 295 to 309 mosm/liter.

Elevation of tear osmolarity suggests dry eyes. . It is a very sensitive test for identifying a dry eye but lacks specificity. The test often is not used because of the lack of commercially available equipment for its measurement.[21]

Tear Lactoferrin Test

There is a decrease in lactoferrin levels in the reflex tear secretion of dry eyes. The test include Lactoplate, a radio immuno diffusion assay and an ELISA based test requiring only 10-15 minutes.

Tear Lysozyme Test

Tear Lysozyme is a useful measure of the aqueous tear secretion since it constitutes nearly ¼ of the total tear secretion proteins.

Patients with Sjogren's sydrome have decreased lysozyme production. Several methods – microbiological, turbidimetric and spectrometric assays – are used to determine the level of lysozyme in tears. Normal tear lysozyme levels are between 2 and 4 mg per ml.

Ocular Ferning Test

The ocular ferning test is a simple, inexpensive qualitative test of the conjunctival mucus that is performed by spreading conjunctival scrapings onto a clean glass slide and allowing the glass slide to dry. Microscopic arborization (ferning) is observed in normal eyes, whereas patients with cicatrizing conjunctivitis such as ocular pemphigoid, Stevens – Johnson syndrome, trachoma, or alkali burn may show decreased mucus production and none or reduced ferning. Ocular ferning may be affected by the presence of salts.

Test Results

The diagnosis of dry eye syndrome is made from a combination of the clinical history, a suggestive constellation of abnormalities on Schirmer's and TBUT testing, fluorescein staining, and rose bengal staining and if available, confirmatory laboratory evidence of increased tear osmolarity and decreased reflex lactoferrin levels.

TREATMENT

Certain therapeutic principles apply to the treatment of dry eye. These include general concepts and specific treatment goals. The most basic principle is the education of the patient to help him or her understand the need for and the rationale behind any recommended therapy. A patient's attitude toward dry eye is one of the most important determinants of compliance with treatment. Lack of compliance is certainly a predictor of failure for any treatment. Explanation of the fact that the patient's tear film is not effectively protecting the surface of the eye helps in the understanding of which factors aggravate the condition and why certain specific treatments are recommended. It also helps to explain that some treatments are palliative whereas others attempt to correct a specific abnormally that contributors to the dry eye. Alerting patients to environmental conditions that aggravate dry eye (air- conditioning, airplane travel) and activities that provoke tear film instability (reading, computer use, fatigue) will help them adjust their environment or adapt their treatments to times of greatest stress on the tear film.[82]

Eliminating aggravating factors

Many patients with aqueous tear deficiency also have concurrent meibomian gland disease.[83-85] Control of meibomian gland disease with a vigorous lid hygiene and lid massage regimen and treatment of concurrent blepharitis often provide effective relief for the symptoms of dry eye, particularly in the patient with mild aqueous deficiency.[86] If the meibomian gland disease is resistant to mechanical therapy alone, oral doxycycline (100 mg per day by mouth) will often add to the success of lid message.[87]

It is also important to recognize any abnormality in cyclic blinking or nocturnal exposure that might cause inadequate tear film distribution or increased evaporation. If such exposure is identified, using nocturnal ointment lubrication or taping the eyelid closed at night may be necessary.

Certain systemic medications atropine, anthistaminics, hypnotics, phenothiazines and psychotropic agents can also decrease tear production and aggravate dry eye. Minimization of the drug dose or use of an alternative therapy is advisable. Use of ophthalmic solutions without preservatives should be ensured in patients with severe dry eyes syndrome as perservatives can aggravate ocular surface disorders.

Avoidance of contact lenses with high water content such as the soft contact lenses as they dehydrate the cornea and decrease tear production possibly due to decreased corneal sensation.

Replacing the tear volume

The therapy most often invoked for dry eye is a supplement tear lubricant. This is palliative therapy, but it is often effective for the patient with mild to moderate dry eye. Numerous artificial tear preparations are available.[88-90] A recent variation on the lubricant has been the use of hypotonic solutions to mitigate the hyperosmotic property of tears in the patient with dry eye.[91-92] Although the effect of hypotonic lubricant instillation is transient, some patients respond well to this formulation.

Preservation of the tear film

When supplementation of the tear film is inadequate to control the symptoms or signs of ocular surface damage, attempts to preserve the tear film and to reduce evaporation are appropriate therapy. Fitting spectacles with side shields can improve comfort.

Punctal occlusion is the most often used method to retain and preserve tears. The puncta can be occluded temporarily by collagen stents, but these are usually too transient to provide long-term tear retention. Various temporary punctual plugs are available to close the lacrimal puncta and they typically have a mushroom shape to increase retention. These plugs are usually well tolerated, but occasionally they can provoke a mild inflammatory response around the puncta that can progress to granulation tissue.[93] One caution is that the use of a punctual plug in a patient with inflammatory dry eye, particularly active Sjogren syndrome, may result in increased irritation because the retention of proinflammatory mediators and cytokines.[94] Temporary punctual occlusion is preferred before permanent closure of the puncta. Permanent closure is by use of thermal or electrocautery procedures. Laser treatment of the puncta also can be used to occlude the opening.

Stimulation of tear secretion

Although the stimulation of tear production seems a reasonable treatment for dry eye, side effects have limited the usefulness of such stimulants and have been associated with severe adverse events such as anaphylaxis and death. Oral pilocarpine is available to treat the symptoms of dry eye and dry mouth. Side

effects of sweating and diarrhea often limit tolerance to the medication, but the improvement in symptoms has been documented in at least two studies.[95-96] Cevimelin is approved in the United States for treatment of the symptoms of dry mouth and though not approved for the treatment of dry eye, it is better tolerated than pilocarpine and appears effective in xerostomia and keratoconjunctivitis sicca at the 30-mg dose.[97] Laboratory investigation have shown that topical agents that increase cyclic nucleotide levels can stimulate tear secretion, but none of these agents has advanced to clinical trails.[98] A promising medication to increase aqueous tear volume and stimulate mucin secretion is a novel P2Y2 receptor agonist. This topical agent has been shown to increase the flow of sodium and water across conjunctival membranes and to stimulate mucin production from goblet cells.[99] Preliminary clinical trials demonstrate an amelioration of clinical symptoms and signs of surface staining in patients with dry eye. It is not yet approved for the treatment of dry eye disease.

Treating the inflammatory cause of dry eye

Recognition of the role of inflammation in the production of dry eye by the suppression of secretion and damaging effects on the lacrimal glands and ocular surface led to the recommendations of anti-inflammatory therapy for dry eye disease. Unpreserved topical corticosteriods have been effective therapy to reduce inflammation and to improve ocular surface health in patients with dry eye.[100] Unfortunately the long-term side effects of topical corticosteriods, including cataracts and steroid-responsive glaucoma, preclude the use of steroids for long-term treatment of dry eye. Steroids nevertheless are useful in short-term treatment to suppress an acute flare-up of surface inflammation.

More encouraging for long-term therapy is topical cyclosporin A. This immunosuppressive has numerous effects on T cells and it suppresses inflammatory activity and the expression of immune mediator receptors.[101] Clinical trials investigating the safety and effectiveness of topical cyclosporine have demonstrated safety in all trials. Topical cyclsporine received FDA approval in December, 2002 as Restasis (Allergen, Inc, Irvine CA). Although 17% of patients reported some stinging with the instillation of cyclosporine, only 6% of patients discontinued therapy as a result of the discomfort.

Hormonal support therapy is the most recent area of investigation in the clinical treatment of dry eye. The strong laboratory evidence associating decreased androgen levels with lacrimal gland inflammation and lacrimal insufficiency suggest that androgen supplementation is a worthwhile therapy for dry eye disease. Clinical trials evaluating topical testosterone are in phase 2 trials, and though the medication is well tolerated, the studies are yet unmasked is well respect to efficacy.

Another approach to reducing the inflammation associated with dry eye has been through alternative medicine. Anecdotal evidence suggests that herbal or fish-oil derivatives that contain omega-6 essential fatty acids may improve the symptoms of dry eye and tear film stability (Paul Honan, personal communication, 2001). One Scandinavian study suggested improvement in the inflammatory features of Sjogren syndrome by oral administration of gamma-linolenic acid from oil of primrose.[101] An oral commercial medication (Hydroeye; science Based Health) containing gamma-linolenic acid as a source of omega-6 essential fatty acid, a mucin complex, and nutrients including vitamins A, C and

B complex, is marketed for the treatment of dry eye disease. Prospective, Randomized, masked clinical trials have not yet verified efficacy, but some patients report improvement in symptoms. It is unclear whether the essential fatty acids, when effective, improve tear film function through a beneficial effect on lacrimal secretion, the ocular surface, or improved meibomian gland secretion.

The future of anti-inflammatory therapy for the treatment of dry eye disease may well evolve to a combination of acute of topical steroid, long-term immunosuppression, hormonal support, and nutritional supplementation. It is apparent that no one approach is universally efficacious, but control of inflammation does appear to have a role in the management of dry eye disease.

Autologous serum therapy

The use of topical application of autologous serum can be beneficial in patients with severe dry eye when other treatments have failed.[102] It is unclear that the serum contains proteins, peptides, nutrients and growth factors that protect and heal the ocular surface. Identification of the specific molecules responsible for the healing effect of serum may allow more specifically targeted therapy in the future, but the use of the autologous serum technique is workable despite it being cumbersome.

Palliative treatments that historically have been the mainstay of therapy for eye continue to improve and are still appropriate therapy while we await new advances to control the underlying cause of dry eye disease. The approach of tear supplementation and tear preservations continues to be useful. The goal of tear stimulation or enhancement is elusive, but it may be nearer with the advent of

P2Y2 agonists. The recognized importance of inflammation in producing dry eye through lacrimal gland and ocular surface damage is leading us to novel strategies to immunomodulate the disease and to restore hormonal balance to the ocular surface – lacrimal gland homeostatic cycle. It has taken years of investigation to reach this threshold. The next few years should see promising treatments approved for dry eye disease.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

Study design

One year cross-sectional study.

Place

This study carried out at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum

Source of Data

Patients diagnosed with type 2 diabetes mellitus attending Ophthalmic out patient departments at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Study Period

One year from January 2011 to December 2011.

Sample Size

A total of 117 patients were studied.

Sampling procedure

Considering the prevalence of 54.3% dry eyes among patients with type 2 diabetes mellitus the sample size was calculated based on the following formula.

$n = (Z_\alpha)^2 \, p \, q \, / \, d^2$

Where p (Prevalence) = 50%

q (100 – p) = (100 – 50) = 50

d (Absolute error) = 10%

Therefore, n = 117

Hence a total of 117 cases were considered for the study.

Selection criteria

Inclusion criteria

- Patients diagnosed to have type 2 diabetes (as per ADA criteria) of any duration.
- Age above 40 years.

Exclusion criteria

- Patients with systemic disease and local ocular disease/surface abnormalities as assessed by history and clinical examination, other than diabetes mellitus, which are known to cause dry eye / ocular surface abnormalities.
- Like collagenous diseases like, rheumatoid arthritis.
- Patients with chronic contact lens wearers.

- Patients on local or systemic medications, known to cause dry eyes/ocular surface disorders like, tricyclic antidepressants.
- Patients underwent lasik surgery.

Ethical clearance

Prior to the commencement, the study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the participants fulfilling selection criteria were explained about the nature of the study. A written informed consent was obtained from all the participants before enrollment (Annexure I).

Method of collection of data

After the enrollment, patients were interviewed for the demographic data such as age, sex, occupation. Further the patients were subjected to general and systemic examination and asked for the detailed history of diabetes mellitus such as duration and treatment. These findings were recorded on a predesigned and pretested proforma (Annexure II).

The presenting symptoms of dry eyes was obtained through a validated seven item questionnaire of ocular symptoms relating to dry eye.[10] which included the following questions

- Do your eyes ever feel dry ?
- Do you ever feel a gritty or sandy sensation in your eye?

- Do your eyes ever have a burning sensation ?
- Are your eyes ever red ?
- Do your eyes ever feel watery or tearing ?
- Do you notice much crusting on your lashes ?
- Do your eyes ever get stuck shut?

Presence of symptoms from the dry eye questionnaire were graded as;

- Rarely – At least once in three to four months
- Sometimes – Once in two to four weeks
- Often – At least once a week
- All the time

Presence of one or more symptoms often or all the time was taken as positive.

Ocular examination

Ocular examination included recording visual acuity with snellen's chart (in patients with visual acuity less than 6/60, acuity was recorded as counting fingers at particular distance or hand movements or perception of light or projection of rays).

Detailed anterior segment examination was done under slit lamp. Condition of lids, meibomian glands, conjunctival surface (dryness, congestion). Meibomian gland status was graded[103] as follows;

- Grade 0 – No disease

- Grade 1 – Plugging with translucent serous secretion when compressing the lid margin.
- Grade 2 - Plugging with viscous or waxy white secretion when compressing the lid margin
- Grade 3 - Plugging with no secretion when compressing the lid margin.

Cornea was evaluated in detail for its sheen, surface (superficial punctate keratitis SPK/mucous plaques/filamentary keratis), sensation.

Detailed fundus examination **(**under mydriasis) was done under direct and indirect ophthalmoscopy examination. Diabetic retinopathy if present was classified as;

- Non Proliferative Diabetic Retinopathy (NPDR)
    - Mild – NPDR
    - Moderate – NPDR
    - Severe – NPDR
    - Very severe
- Proliferative diabetic retinopathy (PDR)
- Maculopathy
- Advanced diabetic eye disease

Following this, four diagnostic tests namely, Schirmer's test, tear film break up time, rose Bengal test and conjunctival impression cytology were done to rule out the diagnosis of dry eye.

Schirmer's test

This test was performed before the other tests as it had to be done before instillation of anaesthesia. It was carried out using 5 x 35 mm sterile strips of Whatman No. 41 paper. Patient was made to sit in relatively dark area in a room with fan switched off. The terminal rounded end of the strip was folded at the pre marked area along 90^0 angle. Touching the paper strip directly with the finger was avoided in order to avoid contamination of skin oils. The patient was then asked to look up, lower lid retracted and the test paper inserted in the lower cul de sac at the junction of medial two third and lateral one third of the lid. Adequate care was taken during the procedure to ensure that the paper did not touch cornea, in order to avoid reflex tearing. The patients was asked to keep eye closed for five minutes to avoid loss of tear film by evaporation and to avoid reflex tear secretion which may be brought about by blinking.[69] Then the amount of wetting was measured from the fold till the wetted strip area, in mm. The procedure was performed without instilling anaesthesia.

Interpretation

Measurements of < 10 mm were considered to be positive. Readings ≥ 10 mm were considered as negative.[104]

Tear film break up time

This was considered as time in seconds between the last blink and the appearance of the dry spot. The patient was seated at the slit lamp. A drop of antibiotic solution was placed on a sterile fluorescein strip. This drop mixed with

fluorescein was allowed to fall into the lower cul de sac of the eye. Subject was asked to close the eye for a few seconds, blink several times and move eyes around to thoroughly mix the fluorescein with the tear film and to allow even distribution of dye. Then asked to look straight ahead without blinking. The tear film over the lateral half of cornea was then examined with a broad beam and cobalt blue filter, watching for an area of tear film rupture manifested by a black island within the green sea of fluorescein. The time elapsed between the last blink and appearance of first black spot was termed as tear film break up time and noted in seconds. This kind of measurement was taken for three successive blinks and the mean of this was noted as the final reading.

Interpretation

Break up time of less than 10 second was considered as positive indicative of dry eye. Greater than or equal to 10 seconds was considered as negative.[104]

Rose Bengal test

It is a means of assessing ocular surface damage using the rose Bengal dye. One drop of antibiotic solution was put on a sterile, commercially available rose Bengal strip. This drop was allowed to roll into the lower cul de sac of each eye. After 15 seconds the eye was examined for staining of cornea and conjunctiva. The amount of staining in six areas of eye was then recorded and graded based on modified Von Bijsterveld rose Bengal grading map. A quantitative scale of zero to three was used in each area of the conjunctiva of

each eye. A summation of the points assigned to each area was made for each eye.[105]

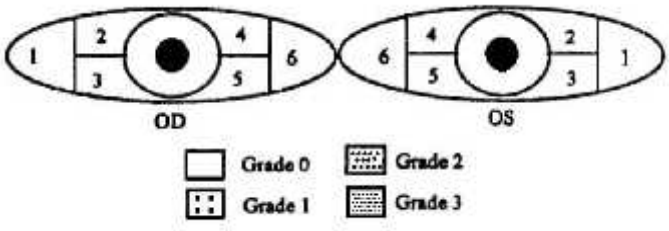


Figure 8. Von Bijsterveld rose Bengal grading map

Interpretation

An additive score of total four or more in the eye constituted a positive test. Less than this value was considered as a negative test.

Conjunctival impression cytology

This is a fool proof method of assessing the ocular surface damage. This test was conducted using cellulose acetate strips having a pore diameter of 28 microns. Just before the test, they were placed in normal saline. Then they were cut to a size of 3 x 10 mm. Proparacain was instilled into the eye. Patient was asked to look towards the nasal side. The strip was then placed on the temporal bulbar conjunctiva using forceps. Gentle pressure was applied using a glass rod with rounded end for eight to ten seconds. Paper was removed using peeling motion and immediately placed on glass slide. The imprint was transferred to the slide by gently rolling the glass rod on it. The slide was placed in a solution containing 95% ethanol (fixative), till further staining.

Four such impressions were taken for each patient, two for each eye. The slides were labeled as A, B, C, D with A and B belonging to right eye and C and D belonging to left eye. Slides A and C were stained using PAS stain. Slides B and D were stained using H and E stain. The slides were interpreted using the grading system described by Nelson.

Interpretation

The eyes having grade 2 or 3 changes were considered positive for dry eye. Eyes with grade 0 or grade 1 were considered negative.[64]

The diagnosis of dry eye was considered when any of two tests were positive.

Grading of dry eye syndrome

- Mild dry eye was defined as patients who have had Schirmer test of less than 10 mm in 5 minutes, T BUT less than 10 seconds.
- Moderate dry eye was defined as Schirmer test of 5 to 10 mm in 5 minutes, T BUT of 5 to 10 seconds.
- Severe dry eye was defined as the Schirmer values in patients less than 5 mm in 5 minutes and T BUT less than 5 seconds.

Statistical analysis

The data was coded and compiled on Microsoft Excel spreadsheet. Categorical data was expressed in terms of rates, ratios and percentages.

Continuous variables were expressed as mean ± standard deviation (SD). The data was analysed by test of proportion and chi-square test. A probability value ('p' value) of < 0.05 was considered as statistically significant.

Chapter 5

Results

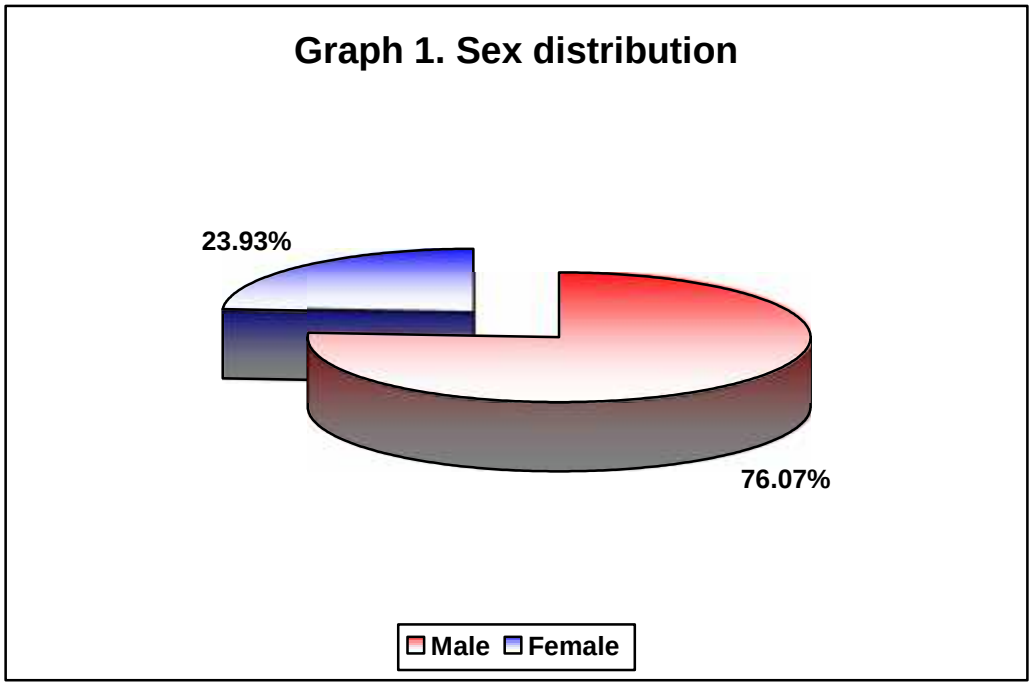
RESULTS

The present one year cross-sectional study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

A total of 117 patients diagnosed with type 2 diabetes mellitus were studied. The data was coded and compiled on Microsoft Excel spreadsheet and analysed. The results obtained were tabulated as below.

Table 1. Sex distribution

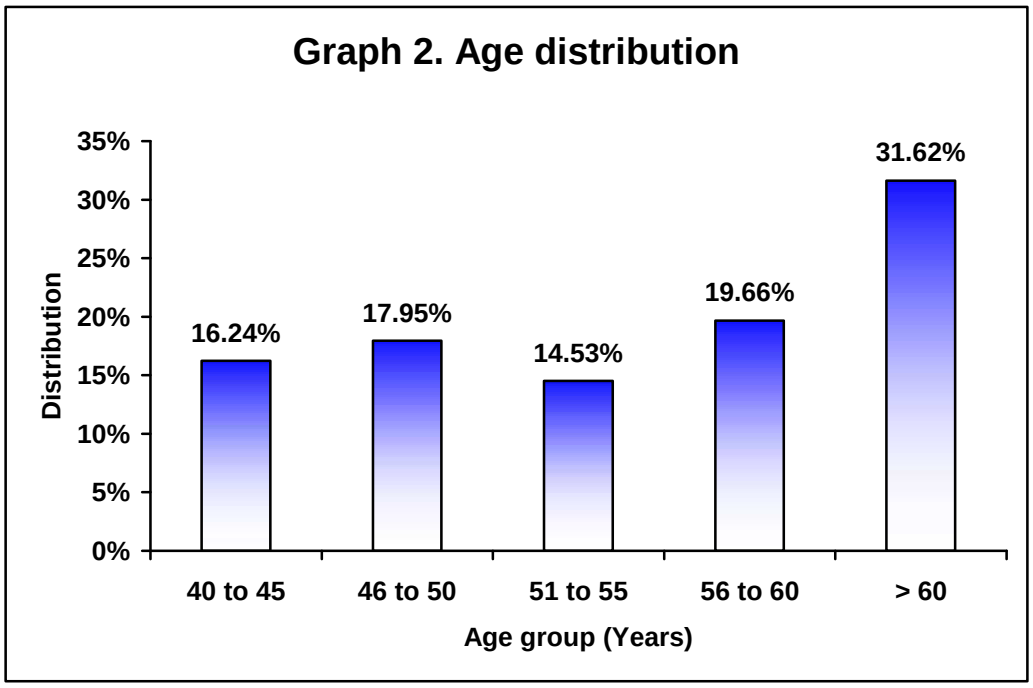
Sex	Distribution (n=117)	
	Number	**Percent**
Male	89	76.07
Female	28	23.93
Total	**117**	**100.00**



In the present study majority of the patients (76.07%) were males and 23.93% were females with male to female ratio of 3.17:1.

Table 2. Age distribtuion

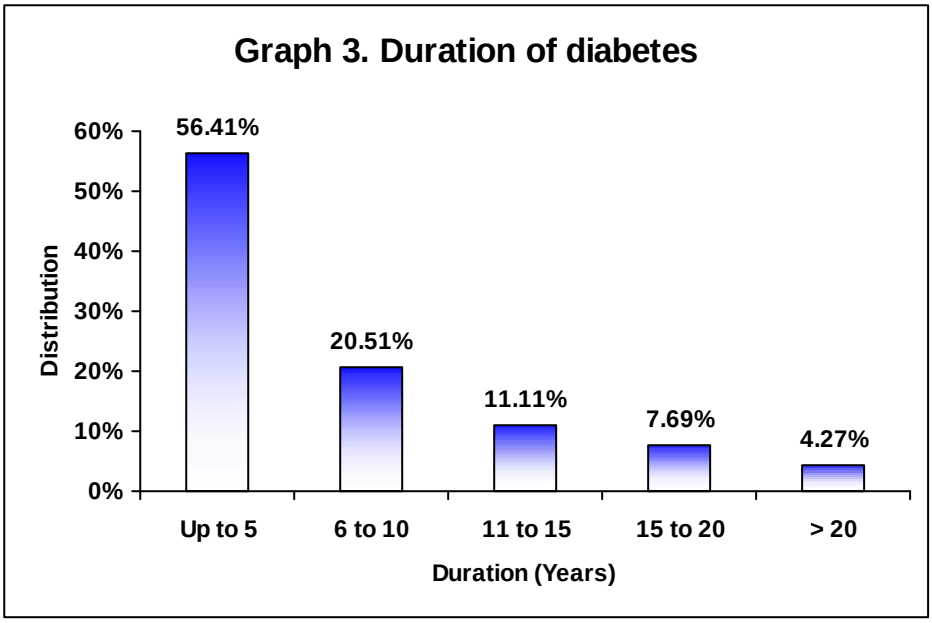
Age group (Years)	Distribution (n=117)	
	Number	**Percent**
40 to 45	19	16.24
46 to 50	21	17.95
51 to 55	17	14.53
56 to 60	23	19.66
> 60	37	31.62
Total	**117**	**100.00**



In the present study most of the patients (31.62%) were aged more than 60 years followed by 56 to 60 (19.66%), 46 to 50 (17.95%), 40 to 45 (16.24%) 51 to 55 (14.535) years. Overall, the mean age was 56.44 ± 9.10 years and the median age was 56 years with range being 40 to 74 years.

Table 3. Duration of diabetes

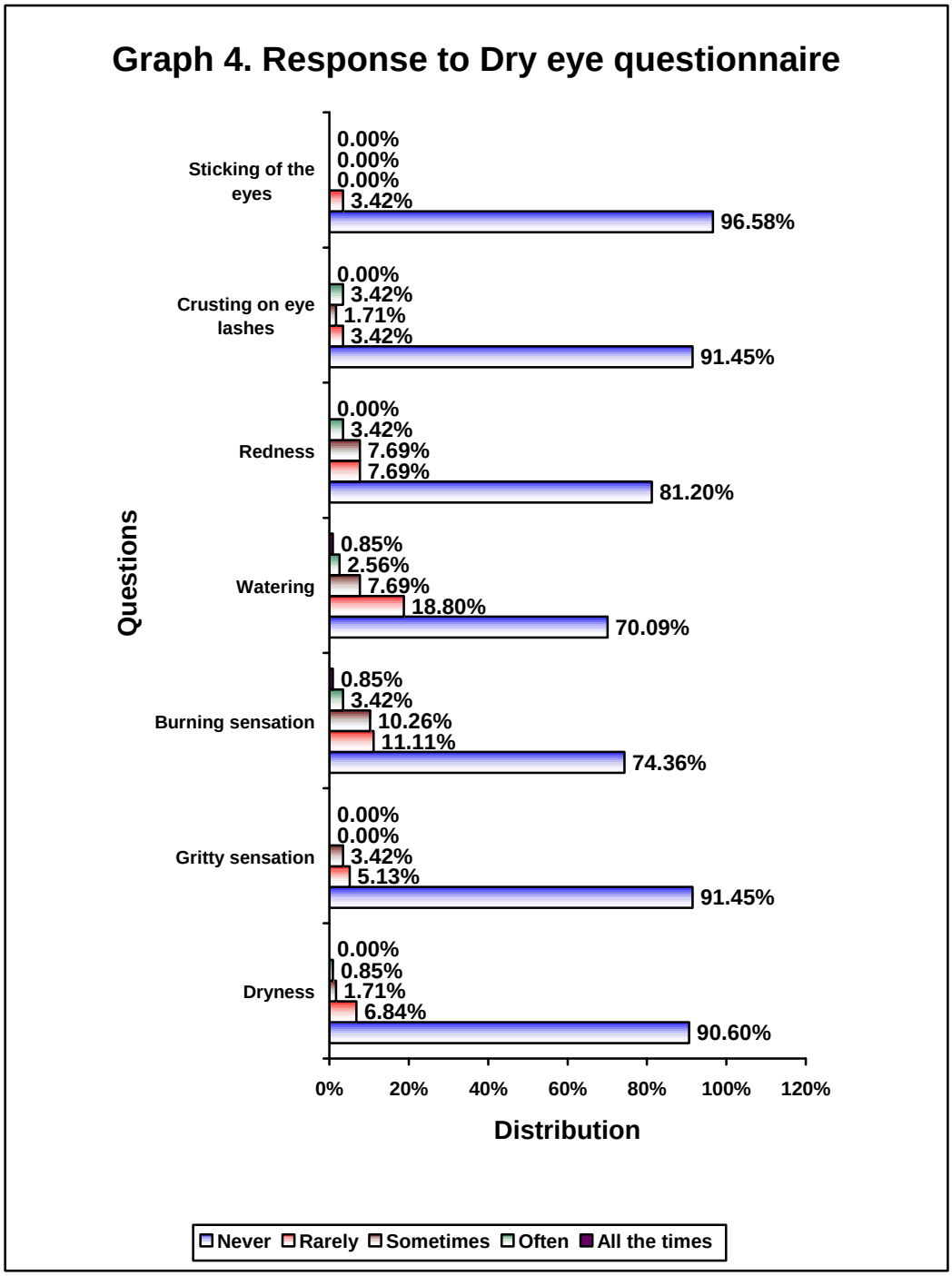
Duration (Years)	Distribution (n=117)	
	Number	Percent
Upto 5	66	56.41
6 to 10	24	20.51
11 to 15	13	11.11
16 to 20	9	7.69
> 20	5	4.27
Total	**117**	**100.00**



In the present study more than half (56.41%) patients had duration of diabetes upto five years. Among 20.51% of patients the duration ranged from 6 to 10 years, in 11.11% 11 to 15 years, in 7.69% patients 15 to 20 years and in 4.27% patients the duration was more than 20 years. Overall, mean duration was 7.00 ± 6.77 years and the median duration was 30 years with range being one year to 30 years.

Table 4. Response to Dry eye questionnaire

Questions	Response (n=117)									
	Never		Rarely		Sometimes		Often		All the times	
	No	%	No	%	No	%	No	%	No	%
Dryness	106	90.60	8	6.84	2	1.71	1	0.85	0	0.00
Gritty sensation	107	91.45	6	5.13	4	3.42	0	0.00	0	0.00
Burning sensation	87	74.36	13	11.11	12	10.26	4	3.42	1	0.85
Watering	82	70.09	22	18.80	9	7.69	3	2.56	1	0.85
Redness	95	81.20	9	7.69	9	7.69	4	3.42	0	0.00
Crusting on eye lashes	107	91.45	4	3.42	2	1.71	4	3.42	0	0.00
Sticking of the eyes	113	96.58	4	3.42	0	0.00	0	0.00	0	0.00



In this study the symptoms of dry eyes were assessed using seven item questionnaire. The responses of the patients are as shown in table 4 and graph 4.

Table 5. Visual acuity

Vision	Right eye (n=117)		Left eye (n=117)	
	Number	**Percent**	**Number**	**Percent**
6/6 to 6/9	43	36.75	45	38.46
6/12 to 6/18	38	32.48	32	27.35
6/24 to 6/36	19	16.24	22	18.80
6/60	6	5.13	6	5.13
Counting finger 3 meters to 1 meter	5	4.27	7	5.98
Counting finger close to face to hands movement close to face	5	4.27	4	3.42
Perception of light and projection of rays	1	0.85	1	0.85
Total	**117**	**100**	**117**	**100**

In the present study most of the patients (36.75%) had visual acuity of 6/6 to 6/9 in the right eye and 38.46% in the left eye. Visual acuity of 6/12 to 6/18 in right eye was recorded among 32.48% patients and 27.35% in left eye.

Table 6. Ocular examination findings

Findings	Right eye (n=117)		Left eye (n=117)	
	Number	**Percent**	**Number**	**Percent**
Eye lashes - Blepharitis	8	6.84	8	6.84
Meibomitis	3	2.56	3	2.56
Lacrimal puncta - Stenosed	1	0.85	1	0.85
Conjunctiva - Dull	21	17.95	21	17.95
Conjunctiva - Congested	4	3.42	4	3.42
Superficial punctate keratitis	1	0.85	2	1.71

The ocular examination findings revealed majority of the patients (17.95%) with dull conjunctiva. Blepharitis was noted among 6.84% patients. Meibomitis grade 2 was seen in 2.56% patients. The congested conjunctiva was noted in 3.42% patients. Few patients (0.85% each) had stenosed lacrimal puncta and superficial punctate keratitis.

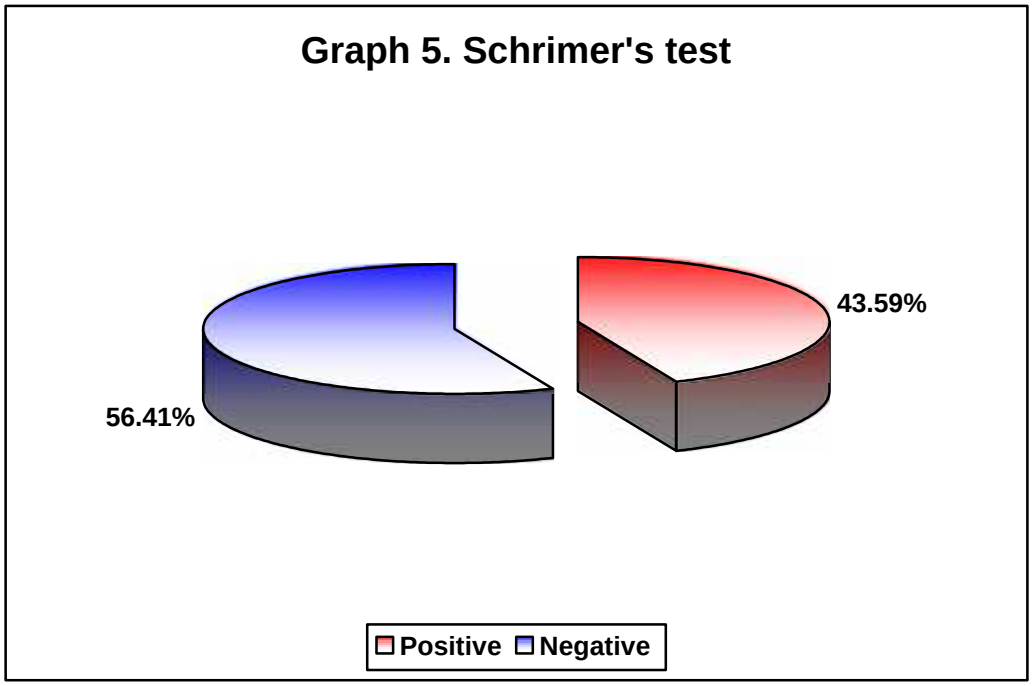
Table 7. Fundus examination

Diabetic retinopathy	Right eye (n=117)		Left eye (n=117)	
	Number	**Percent**	**Number**	**Percent**
No diabetic retinopathy	60	51.28	60	51.28
Mild non proliferative diabetic retinopathy	31	26.50	29	24.79
Moderate non proliferative diabetic retinopathy	14	11.97	14	11.97
Severe non proliferative diabetic retinopathy	2	1.71	2	1.71
Very severe non proliferative diabetic retinopathy	2	1.71	2	1.71
Proliferative diabetic retinopathy	5	4.27	5	4.27
Hazy media	3	2.56	5	4.27
Total	**117**	**100.00**	**117**	**100.00**

In this study 51.28% patients did not had diabetic retinopathy. Among 2.56% of patients in the right eye and 4.27% in the left eye the diabetic retinopathy could not be assessed due to hazy media. In the remaining, 26.5% had mild, 11.97% had moderate, 1.71% each had severe and very severe non proliferative diabetic retinopathy in both the eyes. The proliferative diabetic retinopathy was seen in 4.27% patients in both the eyes.

Table 8. Schrimers test

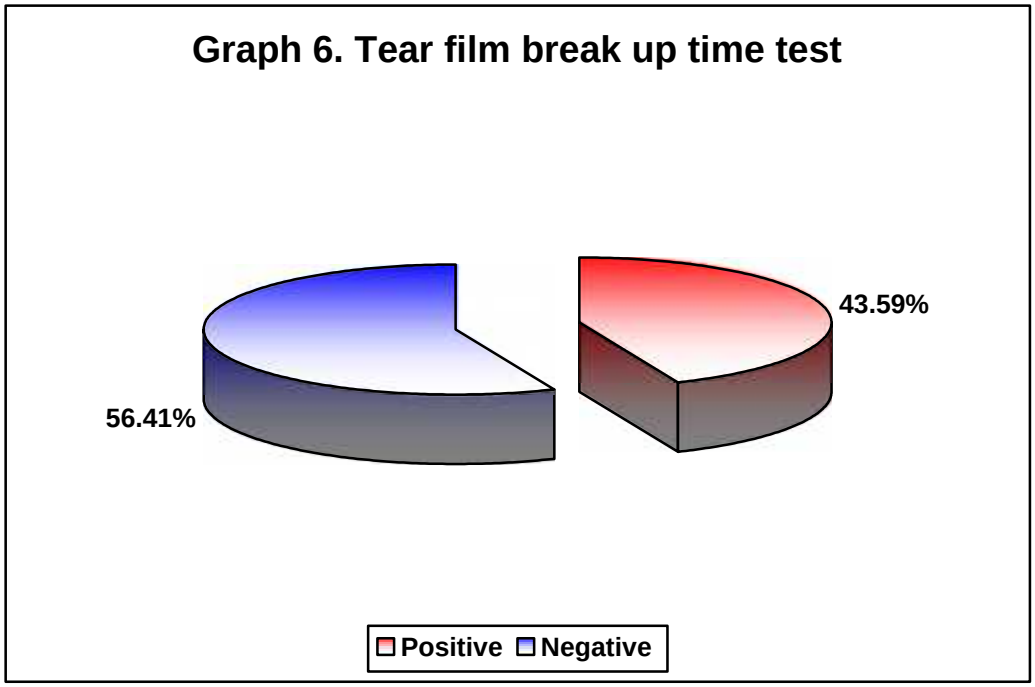
Results	Distribution (n=117)	
	Number	**Percent**
Positive	51	43.59
Negative	66	56.41
Total	**117**	**100.00**



In the present study the Schirmer's test for dry eye syndrome was positive among 43.59% of patients.

Table 9. Tear film break up time test

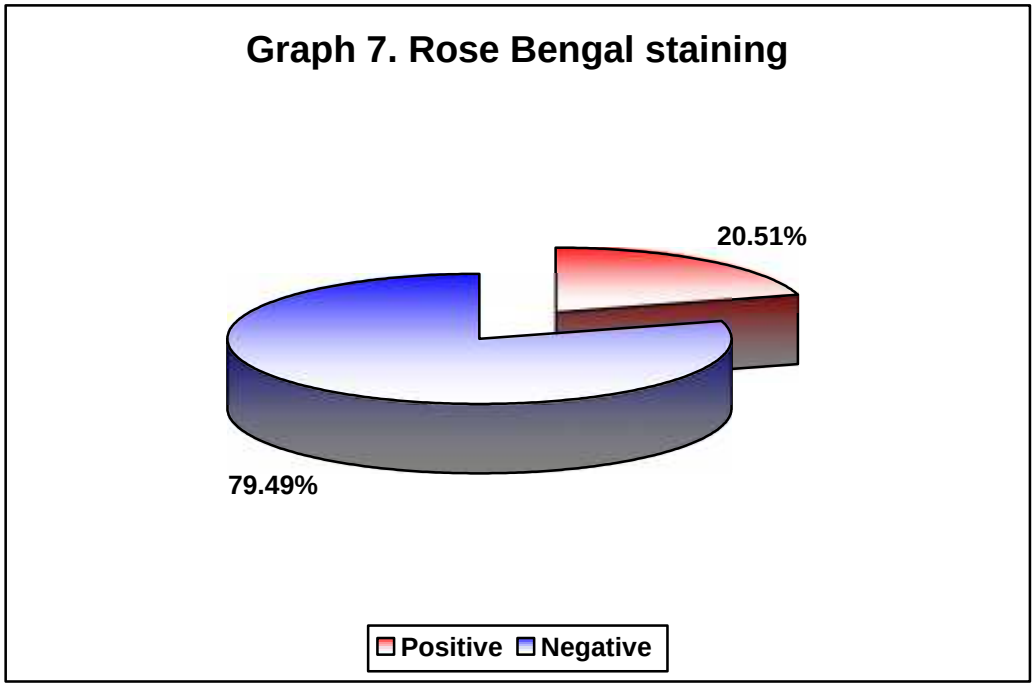
Results	Distribution (n=117)	
	Number	**Percent**
Positive	51	43.59
Negative	66	56.41
Total	**117**	**100.00**



The tear film break up time test for dry eye syndrome was positive in 43.59% of patients.

Table 10. Rose Bengal staining

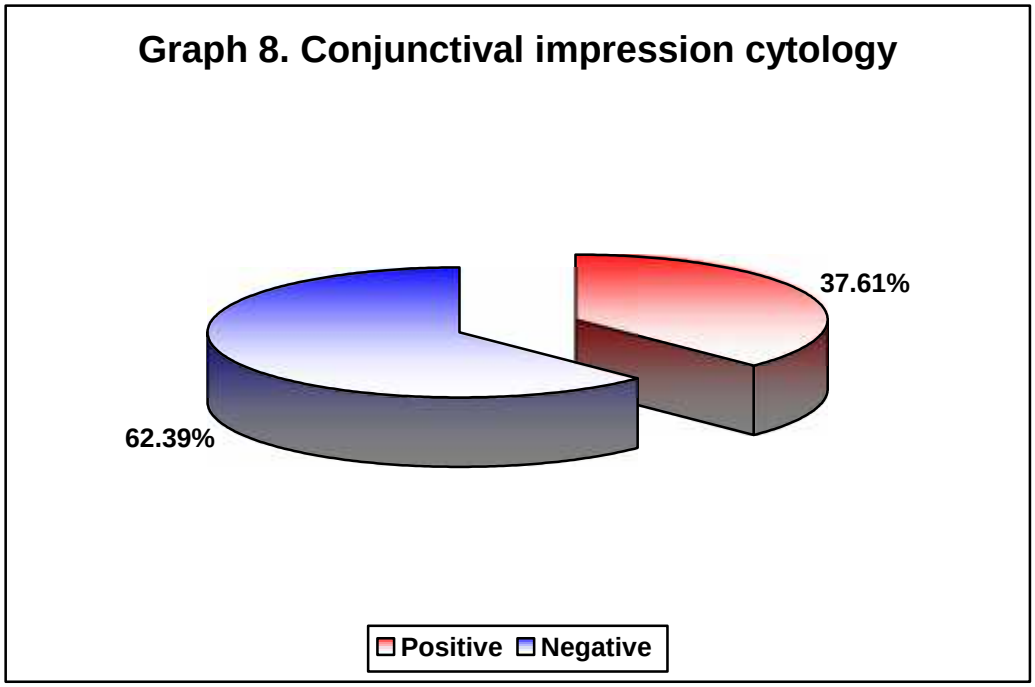
Results	Distribution (n=117)	
	Number	**Percent**
Positive	24	20.51
Negative	93	79.49
Total	**117**	**100.00**



The Rose Bengal test for dry eye syndrome was positive in 20.51% patients.

Table 11. Conjunctival impression cytology

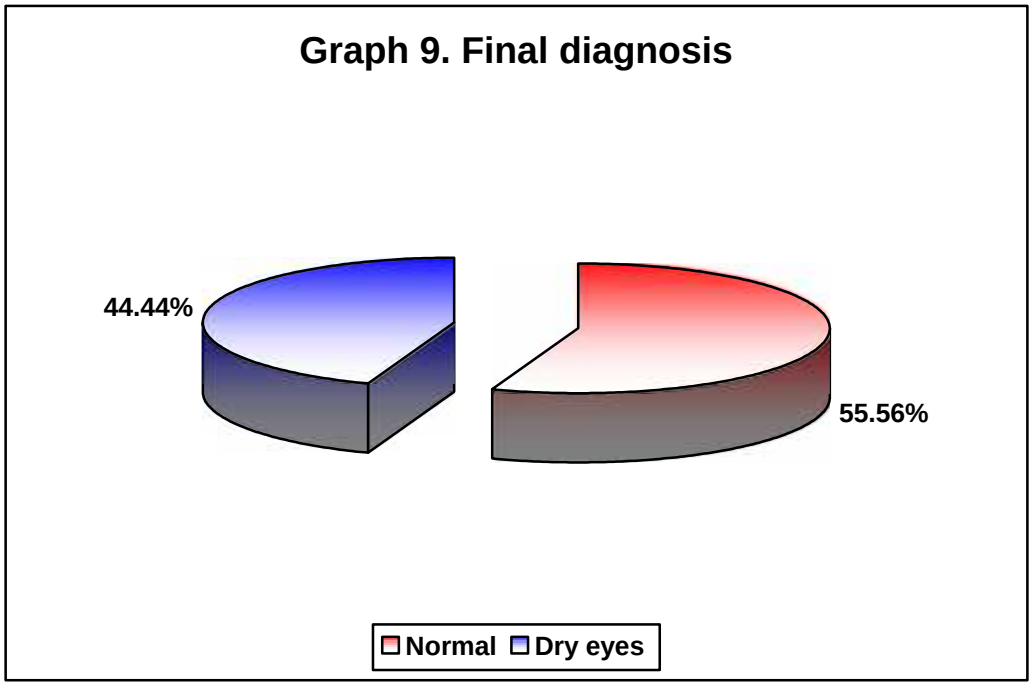
Results	Distribution (n=117)	
	Number	**Percent**
Positive	44	37.61
Negative	73	62.39
Total	**117**	**100.00**



In this study the conjunctival impression cytology was positive among 37.61% of patients.

Table 12. Final diagnosis

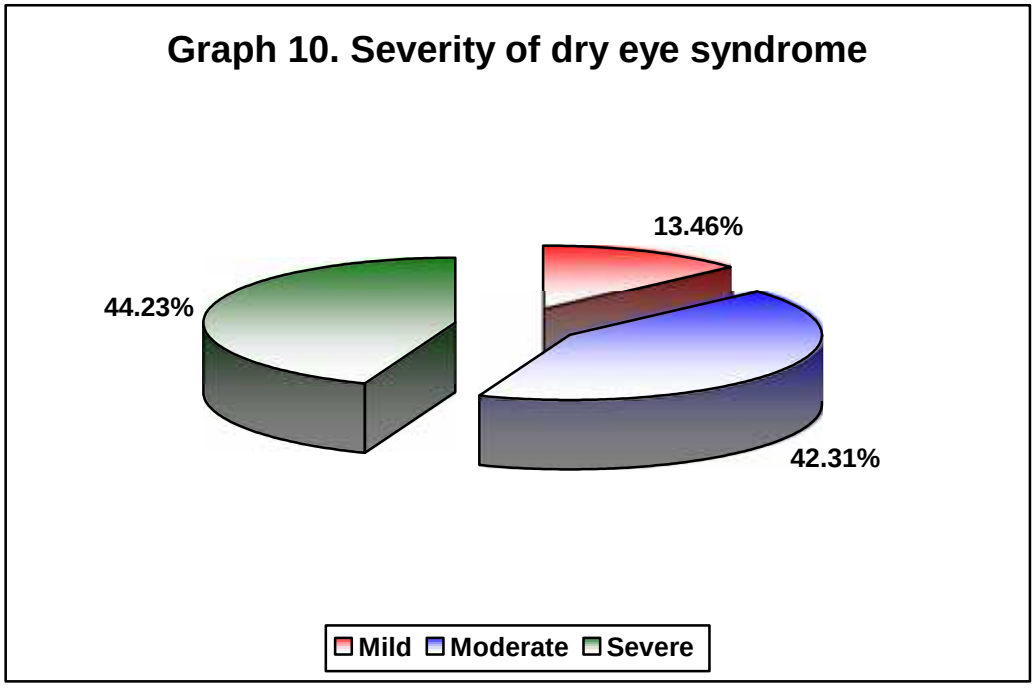
Diagnosis	Distribution (n=117)	
	Number	**Percent**
Normal	65	55.56
Dry eyes	52	44.44
Total	**117**	**100.00**



In the present study out of 117 patients with type 2 diabetes mellitus, 52 (44.44%) had dry eye syndrome.

Table 13. Severity of dry eye syndrome

Severity	Distribution (n=52)	
	Number	**Percent**
Mild	7	13.46
Moderate	22	42.31
Severe	23	44.23
Total	**52**	**100.00**



Of the 52 patients with dry eye syndrome 7 (13.46%) had mild, 22 (42.31%) had moderate and 23 (44.23%) had severe dry eye syndrome.

Table 14. Association of dry eyes with sex

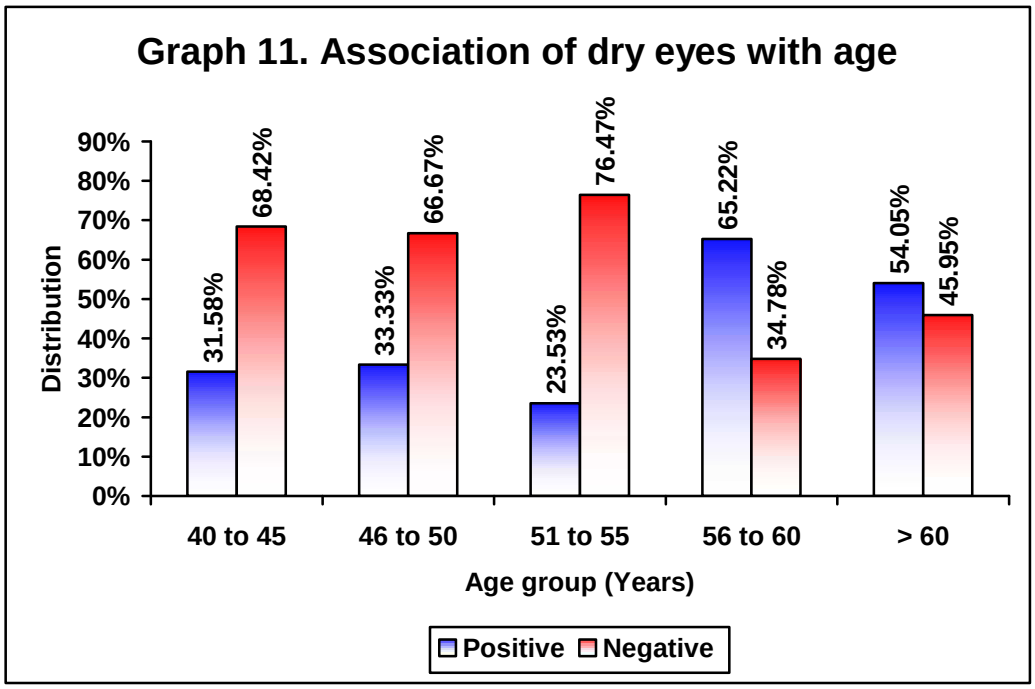
Sex	Positive (n=52)		Negative (n=65)		Total (n=117)	
	Number	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Male	40	44.94	49	55.06	89	100.00
Female	12	42.86	16	57.14	28	100.00
$x^2 = 0.376$			DF = 1		p = 0.846	

In the present study, of the 52 patients with dry eye syndrome, 40 (44.94%) were male and 12 (42.86%) were females suggesting higher proportion of males with dry eye syndrome compared to females. However this difference was statistically not significant.

Table 15. Association of dry eyes with age

Age group (Years)	Positive (n=52)		Negative (n=65)		Total (n=117)	
	Number	Percent	Number	Percent	Number	Percent
40 to 45	6	31.58	13	68.42	19	100.00
46 to 50	7	33.33	14	66.67	21	100.00
51 to 55	4	23.53	13	76.47	17	100.00
56 to 60	15	65.22	8	34.78	23	100.00
> 60	20	54.05	17	45.95	37	100.00

x^2 =10.7 **DF = 4** **p = 0.03**

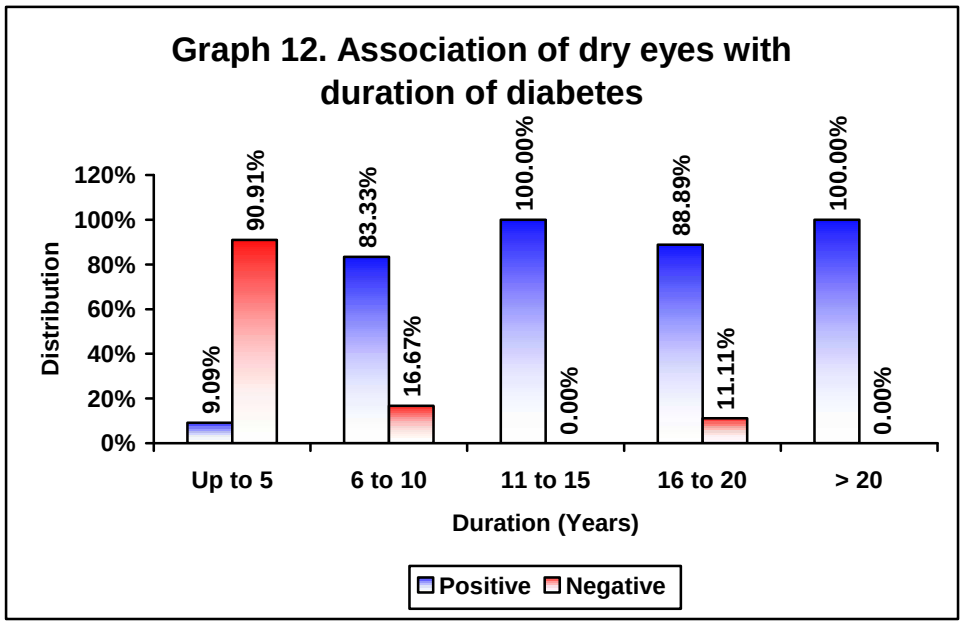


In this study 65.22% patients with dry eye syndrome had age between 50 to 60 years and 54.05% were aged more than 60 years suggesting statistically significant association of increased age as a risk factor for dry eye syndrome.

Table 16. Association of dry eyes with duration of diabetes

Duration (Years)	Positive (n=52)		Negative (n=65)		Total (n=117)	
	Number	Percent	Number	Percent	Number	Percent
Upto 5	6	9.09	60	90.91	66	100.00
6 to 10	20	83.33	4	16.67	24	100.00
11 to 15	13	100.00	0	0.00	13	100.00
16 to 20	8	88.89	1	11.11	9	100.00
> 20	5	100.00	0	0.00	5	100.00

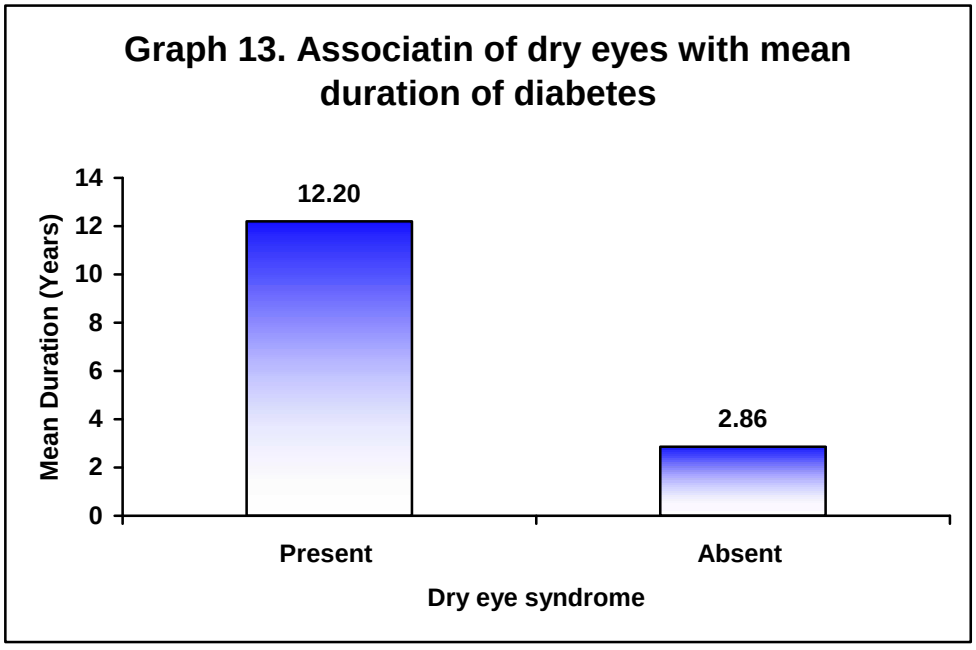
x^2 = 77.8 **DF = 4** **p < 0.0001**



In the present study all the patients (100%) with duration of more than 20 years and 11 to 15 years had dry eye syndrome. Similarly 88.89% of patients with age between 16 to 20 years and 83.33% with 6 to 10 years had dry eye syndrome showing positive association between increasing duration of the diabetic disease and dry eye syndrome.

Table 17. Association of dry eyes with mean duration of diabetes

Duration (Years)	Positive (n=52)	Negative (n=65)
	Mean	**Mean**
Mean	12.2	2.86
SD	6.67	2.87
Median	11	2
Minimum	0.5	0
Maxiumum	30	18
t = 10.2	**DF = 115**	**p < 0.0001**

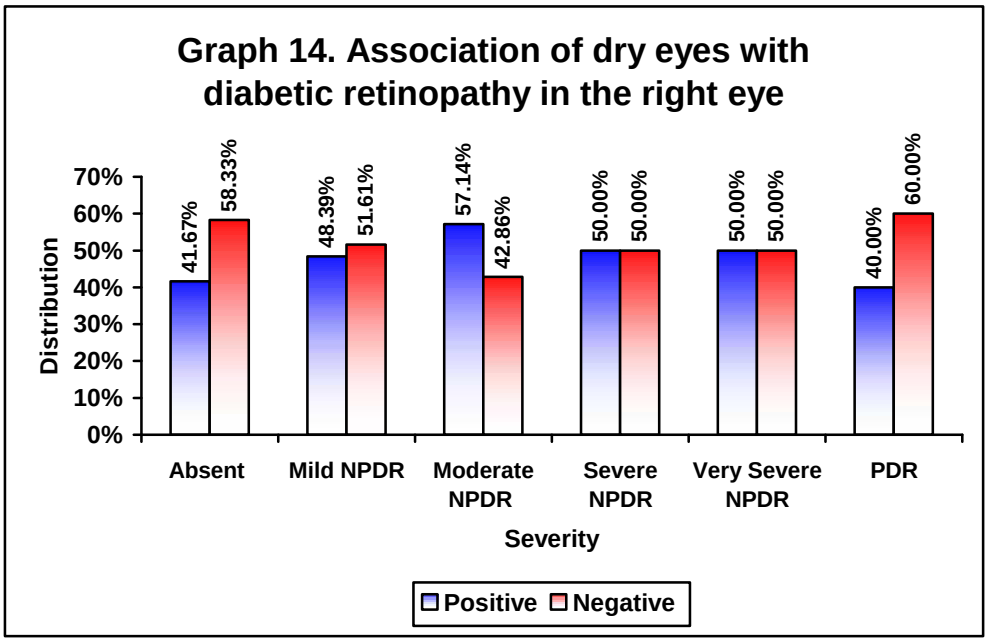


The mean duration of diabetes in patients with dry eye syndrome was significantly high (12.20 ± 6.67 years) compared to those who did not had dry eye syndrome (2.86 ± 2.87 years).

Table 18. Association of dry eyes with diabetic retinopathy in the right eye

Diabetic retinopathy	Positive (n=52)		Negative (n=65)		Total (n=117)	
	No.	%	No.	%	No.	%
No diabetic retinopathy	25	41.67	35	58.33	60	100
Mild non proliferative diabetic retinopathy	15	48.39	16	51.61	31	100
Moderate non proliferative diabetic retinopathy	8	57.14	6	42.86	14	100
Severe non proliferative diabetic retinopathy	1	50.00	1	50.00	2	100
Very severe non proliferative diabetic retinopathy	1	50.00	1	50.00	2	100
Proliferative diabetic retinopathy	2	40.00	3	60.00	5	100
Hazy media	0	0.00	3	100.00	3	100

x^2 = 3.79 **DF = 6** **p = 0.705**

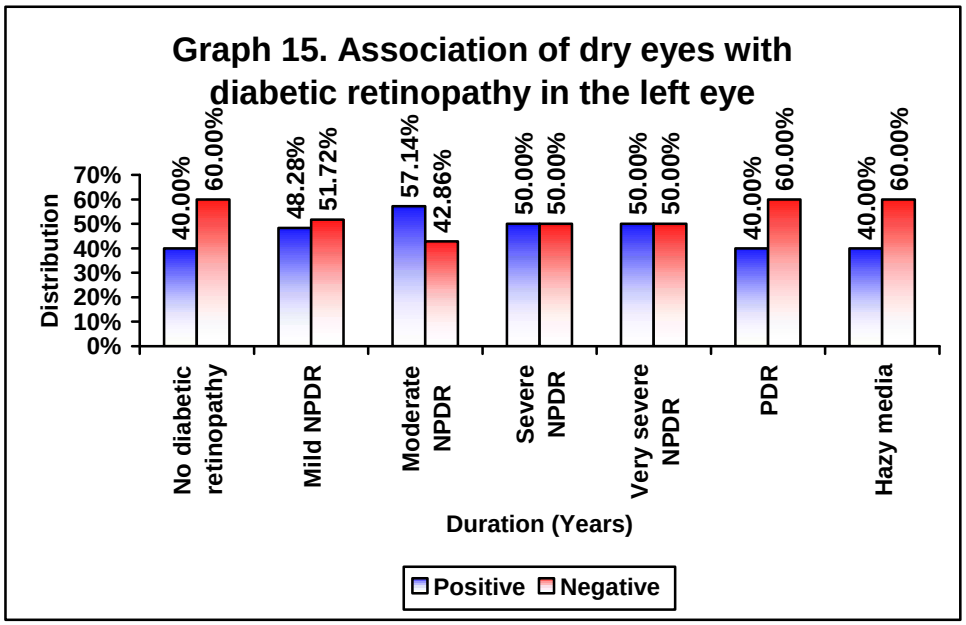


The distribution of dry eye syndrome with different stages of diabetic retinopathy in right eye are as shown in table 18 and graph 14 and no statistically significant association between diabetic retinopathy and dry eye syndrome was noted.

Table 19. Association of dry eyes with diabetic retinopathy in the left eye

Diabetic retinopathy	Positive (n=52)		Negative (n=65)		Total (n=117)	
	No.	%	No.	%	No.	%
No diabetic retinopathy	24	40.00	36	60.00	60	100
Mild non proliferative diabetic retinopathy	14	48.28	15	51.72	29	100
Moderate non proliferative diabetic retinopathy	8	57.14	6	42.86	14	100
Severe non proliferative diabetic retinopathy	1	50.00	1	50.00	2	100
Very severe non proliferative diabetic retinopathy	1	50.00	1	50.00	2	100
Proliferative diabetic retinopathy	2	40.00	3	60.00	5	100
Hazy media	2	40.00	3	60.00	5	100

x^2 = 1.67 **DF = 5** **p = 0.892**



The distribution of dry eye syndrome with different stages of diabetic retinopathy in left eye are as shown in table 18 and graph 14 and no statistically significant association between diabetic retinopathy and dry eye syndrome was noted.

Table 20. Sensitivity of tear film break up time with Schrimer's test

Tear film break up time (n=117)	Schirmer's test (n=117)				Total	
	Positive (n=51)		Negative (n=66)			
	Number	Percent	Number	Percent	Number	Percent
Positive	34	66.67	17	33.33	51	43.58
Negative	17	25.76	49	74.24	66	56.59
Total	**51**	**43.58**	**66**	**56.59**	**117**	**100.00**

Sensitivity = 66.67%; Specificity = 74.24% PPV = 66.67; NPV = 66.67

In the present study Schirmer's test and tear film break up time showed dry eye syndrome among 43.58%. The sensitivity of tear film break up time in detecting dry eye syndrome compared to Schirmer's test was 66.67% with specificity of 74.24%, PPV of 66.67% and NPV of 66.67%

Table 21. Sensitivity of rose Bengal test with Schirmer's test

Rose Bengal Test (n=117)	Schirmer's test (n=117)				Total	
	Positive (n=51)		Negative (n=66)			
	Number	Percent	Number	Percent	Number	Percent
Positive	19	37.25	5	7.57	24	20.51%
Negative	32	62.75	61	92.42	93	79.49%
Total	**51**	**43.58**	**66**	**56.59**	**117**	**100.00**

Sensitivity = 37.25%; Specificity = 92.42%; PPV = 79.17%; NPV = 65.59%

In the present study Schirmer's test showed dry eye syndrome among 43.58% and rose Bengal test showed positive dry eye syndrome among 20.51%. the sensitivity of rose Bengal test in detecting dry eye syndrome compared to Schirmer's test was 37.25% with specificity of 92.42%, PPV of 79.17% and NPV of 65.59%.

Table 22. Sensitivity of conjunctival impression cytology with Schirmer's test

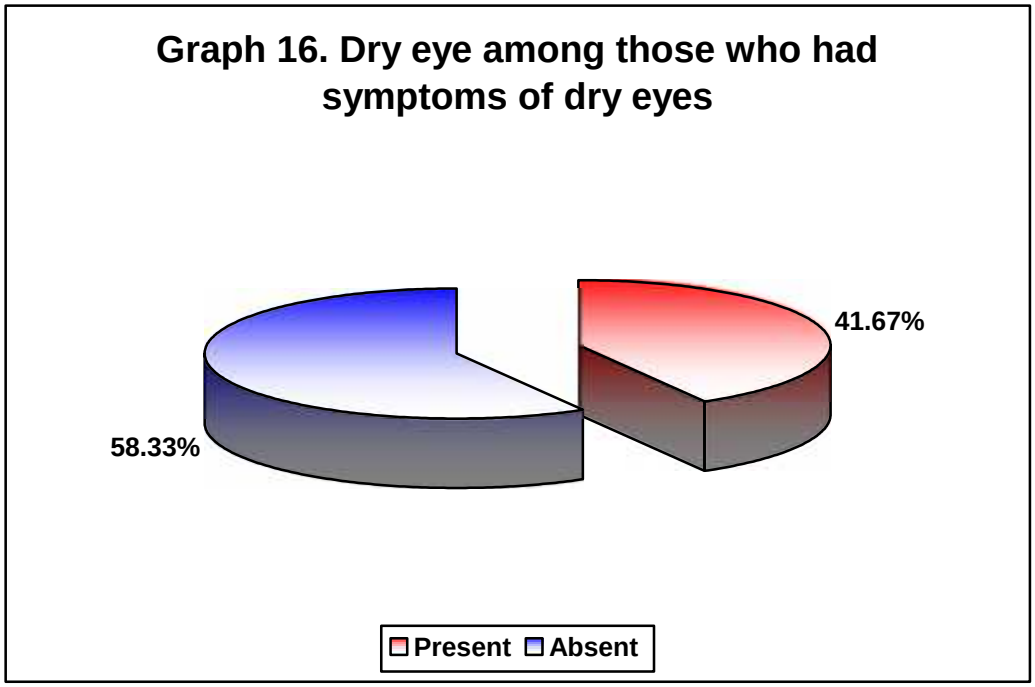
Impression cytology (n=117)	Schirmer's test (n=117)				Total	
	Positive (n=51)		Negative (n=66)			
	Number	Percent	Number	Percent	Number	Percent
Positive	31	70.45	13	29.55	44	37.60
Negative	20	27.40	53	72.60	73	62.40
Total	**51**	**43.58**	**66**	**56.59**	**117**	**100.00**

Sensitivity = 60.78%; Specificity = 80.30%; PPV =70.45%; NPV = 72.60;

In this study Schirmer's test showed dry eye syndrome among 43.58% and conjunctival impression cytology was positive among 37.60%. The sensitivity of impression cytology in detecting dry eye syndrome compared to Schirmer's test was 60.78% with specificity of 80.30%, PPV of 70.45% and NPV of 72.60%.

Table 23. Dry eyes among those who had symptoms of dry eyes

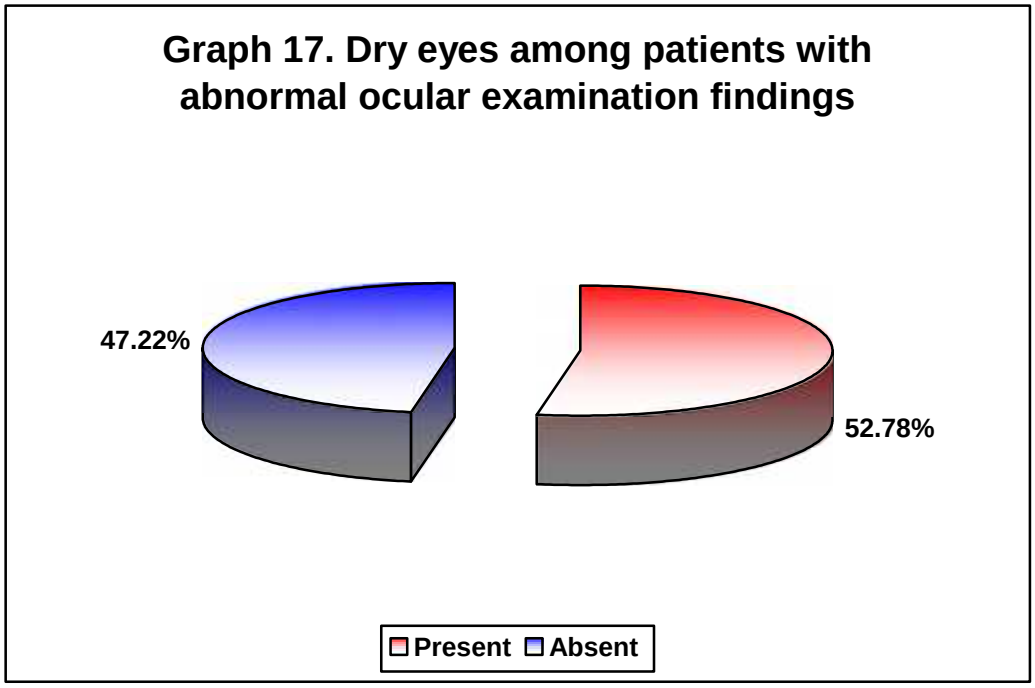
Dry eye syndrome	Distribution (n=12)	
	Number	**Percent**
Present	5	41.67
Absent	7	58.33
Total	**12**	**100.00**



In this study based on seven item questionnaire, 12 patients experienced symptoms often and all the times. Among these seven (58.33%) had dry eye syndrome.

Table 24. Dry eyes among patients with abnormal ocular examination findings

Dry eye syndrome	Distribution (n=36)	
	Number	**Percent**
Present	19	52.78
Absent	17	47.22
Total	**36**	**100.00**



In this study ocular examination revealed abnormal findings among 36 patients. Of these, 19 patients (52.78%) were diagnosed to have dry eye syndrome.

Table 25. Dry eyes among abnormal ocular examination findings

Findings	Dry eye		Absent		Total	
	No.	%	No.	%	No.	%
Eye lashes - Blepharitis	5	62.50	3	37.50	8	100
Meiobian gland opening grade 2	1	33.33	2	66.67	3	100
Lacrimal puncta - Stenosed	0	0.00	1	100.00	1	100
Conjunctiva - Dull	12	57.14	9	42.86	21	100
Conjunctiva - Congested	3	75.00	1	25.00	4	100
Cornea surface - Superficial punctate keratitis	0	0.00	1	100.00	1	100

In the present study of the eight patients with blepharitis in five (62.50%) had dry eye syndrome. Similarly, of the 21 patients with dull conjuctiva, 12 (57.14%) had dry eye syndrome.

Chapter 6

Discussion

DISCUSSION

Diabetes is often associated with several significant ocular conditions, such as retinopathy, refractive changes, cataract, nerve palsies, glaucoma and macular edema. Diabetes has rapidly become one of the leading systemic risk factors for dry eye. This present study was an attempt to find out the prevalence of dry eyes in patients of type 2 diabetes and also to study the association of dry eyes with the duration of disease and with the stages of diabetic retinopathy.

The present one year cross-sectional study was conducted on a total of 117 patients diagnosed with type 2 diabetes mellitus in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

In the present study males outnumbered females (76.07% vs 23.93%) with male to female ratio of 3.17:1. Most of the patients (31.62%) were aged more than 60 years followed by 56 to 60 (19.66%). Overall, the mean age was 56.44 ± 9.10 years. More than half (56.41%) patients had duration of diabetes upto five years. Among 20.51% of patients the duration ranged from 6 to 10 years, in 11.11% 11 to 15 years, in 7.69% patients 15 to 20 years and in 4.27% patients the duration was more than 20 years. Overall, mean duration was 7.00 ± 6.77 years.

In the present study most of the patients (36.75%) had visual acuity of 6/6 to 6/9 in the right eye and 38.46% in the left eye. The ocular examination findings revealed majority of the patients (17.95%) with dull conjunctiva. Blepharitis was noted among 6.84% patients. Meibomitis was seen in 2.56%

patients. The congested conjunctiva was noted in 3.42% patients. Few patients (0.85% each) had stenosed lacrimal puncta and superficial punctate keratitis. In this study, 26.5% had mild, 11.97% had moderate, 1.71% each had severe and very severe NPDR in both the eyes. The proliferative diabetic retinopathy was seen in 4.27% patients in both the eyes. However among 2.56% of patients in the right eye and 4.27% in the left the diabetic retinopathy could not be assessed due to hazy media due to cataractous changes.

In the present study the Schirmer's test, tear film break up time test, rose Bengal test and conjunctival impression cytology was positive among 43.59%, 43.59%, 20.51% and 37.61% of patients respectively. Out of 117 patients with diabetes mellitus, 52 (44.44%) had dry eye syndrome. Of the 52 patients with dry eye syndrome 7 (13.46%) had mild, 22 (42.31%) had moderate and 23 (44.23%) had severe dry eye syndrome.

The prevalence of dry eye in the present study was 44.44%. The prevalence of dry eyes varies from 18.1% to 70%, thereby showing wide disparity. Beaver's Dam Eye study[41] reported prevalence of 19.8% in type 2 diabetes mellitus. Another study[106] from Iran reported prevalence of 54.3%. The prevalence reported in the present study was comparable with a study done by Nepp et al.[107] Much of this disparity stems from the fact that there is no standardisation of the types of patients selected for the study, dry eye questionnaires, objective tests and dry eye diagnostic criteria.

In the present study, of the 52 patients with dry eye syndrome, 40 (44.94%) were male and 12 (42.86%) were females suggesting higher prevalence

of dry eye syndrome among males compared to females. However this difference was statistically not significant. Moss et al[39] reported a higher incidence of dry eyes in diabetic women (16.7% compared with 11.4% in men). A study[106] from Iran reported no sex predilection in dry eye syndrome. The possible explanation for this could be the diabetes-induced KCS has no sex predilection, thus weakening the effect of female sex on KCS. Deficient tear secretion from oestrogen deficiency in menopausal women has been hypothesised to explain sex differences, although studies have found that women on hormone replacement therapy may have an increased risk of dry eye.[108]

Various age related changes in lacrimal system occur, including tear chemistry of the tear film. Certain aspects of tear physiology change with age, such as reflex secretion by the lacrimal gland, tear volume, and tear film stability, whereas others remain more or less unchanged, such as basal tear production. The reflex secretion of tears, as measured by Schirmer's I method (without anaesthesia), decreases significantly with increasing age as already was observed by Schirmer[109] in 1903 and by many others thereafter. The tear evaporation rate has not been found to be correlated with age. The evaporation is primarily controlled by the lipid layer of the tear film and lipid layer thickness appears to be constant for different age groups.[110]

In this study 65.22% patients with dry eye syndrome had age between 50 to 60 years and 54.05% were aged between 50 to 60 years suggesting statistically significant association of increased age as a risk factor for dry eye syndrome. In a cohort study[112] on 3722 subjects were aged 48 to 91 years (65 ± 10 years) and

43% male. The overall prevalence of dry eye was 14.4%. Prevalence varied from 8.4% in subjects younger than 60 years to 19.0% in those older than 80 years.[112]

The higher incidence of dry eyes in this age group could be partly attributed to ageing. However in the Beaver Dam Eye study,[41] ageing effect was significant after 65 years of age. Therefore higher prevalence of dry eye in age group 51-60 in the present study could be because of diabetes per se, selection bias could have also contributed to this since higher number of participants were in this age range.

In the present study all the patients (100%) with duration of more than 20 years and 11 to 15 years had dry eye syndrome. Similarly 88.89% of patients with age between 11 to 15 years and 83.33% with six to ten years had dry eye syndrome showing positive association between increasing duration of the diabetic disease and dry eye syndrome. The mean duration of diabetes in patients with dry eye syndrome was significantly high (12.20 ± 6.67 years) compared to those who did not had dry eye syndrome (2.86 ± 2.87 years). In a study[106] from Iran prevalence of dry eye syndrome was significantly higher in patients with longer duration of diabetes. In type II diabetic patients, most of the long term complications of diabetes are well known to correlate with duration, dry eyes could also be a part of this.

For years, most common means of measuring tear production has been schirmer's test. Much disagreement exists as to the validity and usefulness of this test False negative and false positive results cloud the usefulness of each test. Inspite of inconsistent repeatability, this test enjoys widespread use. The present

data suggest that the amount of reflex tearing is more affected in diabetics. It is possible that the decreased amount of reflex tearing in diabetics may be the result of a diminished corneal and conjunctival sensitivity, which has been demonstrated in diabetics by electronic aesthesiometry[112] In a previous fluorophotometric study Stolwijk et al[113] demonstrated a decreased corneal epithelial stability in diabetics after provocation with eye drops containing oxybuprocaine 0.4% and 0.01% benzalkonium chloride, a finding that could be related to the reduced reflex tearing in diabetics.

'Symptoms often do not correlate with signs of dry eyes' is a well known fact. The patient report of dry eye symptoms tends to be more reliable and accurate than many dry eye clinical tests, in addition, the results of dry eye clinical tests tend to agree poorly with patient reported symptoms. This is likely because of significant within- and between-patient variances associated with the reliability of many dry eye tests as well as symptom report. These factors lead to a dilemma in both clinical practice and research, making clinical decisions difficult regarding tests to be used and interpretation of those tests. This has lead to a reliance on symptom-based diagnosis of dry eye.[112]

In this study based on seven item questionnaire, 12 patients experienced symptoms often and all the times. Among these seven (58.33%) had dry eye syndrome. The diabetic patients may exhibit dry eye signs with or without discomfort due to corneal neuropathy.

Each form of dry eye (tear deficient form or evaporative form) has certain global features in common, including a set of characteristic symptoms, ocular

surface damage, reduced tear film stability, and tear hyperosmolarity. Increasingly, an inflammatory component has become apparent, which contributes not only to symptoms, but also to the disease process itself. For the patient, symptoms are the most important aspect of the disorder, whereas dry eye diagnosis depends additionally on the recognition of tear film instability and ocular surface damage. Tear film instability appears to be a component of all forms of dry eye disease, and tear hyperosmolarity is a key mechanism for ocular surface damage. Although these elements are present in most cases of dry eye, clinicians will sometimes encounter patients who have symptoms but minimal ocular surface damage, or signs of surface damage in the absence of symptoms.[115]

The ocular examination revealed abnormal findings among 36 patients. Of these, 17 patients (47.22%) were diagnosed to have dry eye syndrome. Of the eight patients with blepharitis, five (62.50%) had dry eye syndrome. Similarly, of the 21 patients with dull conjunctiva, 12 (57.14%) had dry eye syndrome.

Blepharitis and meibomitis are well known to contribute to evaporative dry eyes. Diabetic patients are prone to develop these more often. There is a possibility that, in some patients, meibomitis may create sufficient conjunctival inflammation to decrease tear secretion by damaging accessory lacrimal gland tissue in the conjunctiva.[23]

In the present study Schirmer's test and tear film break up time showed dry eye syndrome among 43.58%. The sensitivity of tear film break up time in detecting dry eye syndrome compared to Schirmer's test was 66.67% with

specificity of 74.24%, PPV of 66.67% and NPV of 66.67%. Rose Bengal test showed positive dry eye syndrome among 20.51%. The sensitivity in detecting dry eye syndrome compared to Schirmer's test was 37.25% with specificity of 92.42%, PPV of 79.17% and NPV of 65.59%. Conjunctival impression cytology was positive among 37.60%. The sensitivity of conjunctival impression cytology in detecting dry eye syndrome compared to Schirmer's test was 60.78% with specificity of 80.30%, PPV of 70.45% and NPV of 72.60%.

In the present study no statistically significant association was observed between diabetic retinopathy and dry eye syndrome. Earlier study by saito et al,[46] decrease in corneal sensation, but not that in tear secretion, was correlated with the stage of diabetic retinopathy. However, Nepp and associates[45] were able to correlate severity of retinopathy with the severity of dry eyes. Further studies needs to be done to clarify association between these two. In a study[106] from Iran there was significant association between sex and grades of DR. Lower grades of DR was more common in women and higher grades of DR was more common in men, such a relation was found in another study by Rema et al.

Chapter 7

Conclusion

CONCLUSION

The results of the present study showed 44.44% prevalence of dry eye syndrome among patients with type 2 diabetes mellitus.

Dry eye syndrome in patient with type 2 diabetes mellitus was significantly associated with increasing age and longer duration whereas diabetic retinopathy and male:female ratio did not influence the prevalence of dry eye syndrome.

Chapter 8

Summary

SUMMARY

Diabetes is often associated with several significant ocular conditions, such as retinopathy, refractive changes, cataract, nerve palsies, glaucoma and macular edema. However, recently problems involving ocular surface, dryness in particular had been reported. This present study was an attempt to find out the prevalence of dry eyes in patients of type 2 diabetes and also to study the association of dry eyes with the duration of disease and with the stages of diabetic retinopathy.

The present one year cross-sectional study was conducted on a total of 117 patients diagnosed with type 2 diabetes mellitus in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

In the present study majority of the patients (76.07%) were males with male to female ratio of 3.17:1. Most of the patients (31.62%) were aged more than 60 years followed by 56 to 60 (19.66%). Overall, the mean age was 56.44 ± 9.10 years. More than half (56.41%) patients had duration of diabetes upto five years. Overall, mean duration was 7.00 ± 6.77 years In the present study the Schirmer's test, tear film break up time test, Rose Bengal test and conjunctival impression cytology was positive among 43.59%, 43.59%, 20.51% and 37.61% of patients respectively.

The results of the present study showed 44.44% prevalence of dry eye syndrome among patients with type 2 diabetes mellitus. Dry eye syndrome in patient with type 2 diabetes mellitus was significantly associated with increasing

age and longer duration whereas diabetic retinopathy and male: female ratio did not influence the prevalence of dry eye syndrome.

Chapter 9

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Annexures

Annexure I

ANNEXURE I

INFORMED CONSENT FORM FOR STUDY OF DRY EYE IN TYPE 2 DIABETES

Mr. / Ms. / Mrs. ----------, we are requesting you to enroll yourself in the study titled "study of dry eye in type 2 diabetics" conducted by **Dr. **** *****,** post graduate student in M.S Ophthalmology under the guidance of **Dr. **** ******** at J.N Medical college, Belgaum under KLE University, Belgaum.

Tear film is an important part of eye. Loss of tear film due to any cause gives rise to A condition known as dry eye. This study is being undertaken to know, to what extent this dry eye may occur in patients of type 2 diabetes. Patients of type 2 diabetes coming to KLES Dr. Prabhakar Kore hospital will be participating in this study. You are requested to participate into the study group.

Procedure involved

The participants are required to answer a few questions regarding symptoms of dry eye. 4 test will be conducted on them to assess the damage which may have occurred to the outer covering of the eye ball. 4 types of strips will be put into the eye at different times for the study. These tests will be done by experienced doctors.

Risks and Benefits

The instillation of one of the strips and eye drops into the eye may cause some amount of burning sensation which will come down on its own and will not require any special treatment. It will not cause any harm to the eye.

By doing these tests, dry eye which might occur in you can be detected in the early stages. By this, further damage to cornea, conjunctiva and complications which are likely to occur can be prevented.

You will not be required to spend any money for this eye examination. The test will be done free of cost. You will also not receive any free gifts or money for participating in the study.

Alternatives

You will be participating in this study by your own free will. Your decision to participate or not in the study will not affect the treatment given to you in the hospital.

Confidentiality

All information collected about you during the course of the study will be kept confidential to the extent permitted by law. Study records and the information from this study may be published but your identity will be confidential in any publication except:

1. In emergency to protect your rights and welfare.
2. If required by law

Authorization to publish results

The results of this study may be published for medical purposes or given to scientific groups for further research. Your identity will not be revealed at any time. In case you have any questions related to the study, you can contact Dr. **** ******. (***** *****)

In case you have any questions about your rights as a study participant, you can contact Dr. **** ***** (**** -******)

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, undersigned _____ am participating in the study by my own free will. I have the right to withdraw from the study at any time due to any reason. I have read the consent form / had it read out to me in front of witnesses and have understood it. I have the right to ask questions at any time during the study.

Signature of the study participant

Name of Study participant Date

Name and Signature of Witness Date

Name and signature of the investigator Date

Annexures

Annexure II

ANNEXURE II – PROFORMA

"Cross sectional study of prevalence of dry eyes in type 2 diabetics"

A. Particulars of Patient

Name of the participant : IP/OP No.:

Age/Sex:

Address:

B. **History of diabetes**:

- Duration :
- Treatment: ☐ ☐
- Control

C. **Chief complaint**

D. **History of present illness**:

E. DRY EYE QUESTIONNAIRE:

1. Do your eyes ever feel dry?
2. Do you ever feel a gritty or sandy sensation in your eyes?
3. Do your eyes ever have a burning sensation?
4. Do your eyes ever feel watering or tearing?
5. Are your eyes ever red?
6. Do you notice much crusting or discharge on your lashes?
7. Do your eyes get stuck in the morning?

(Allowable response: never, rarely, sometimes, often or all the time)

F. **Past history**

History of hypertension/rheumatoid arthritis/ other systemic illness ☐

History of past ocular surgeries ☐

History of contact lens wear ☐

G. Treatment history: ☐

History of local eye drops usage

History of usage of drugs known to cause dry eyes. ☐

H. Personal history:

Life style / profession/ use of air conditioners/ computers ☐

I. Family history of diabetes: ☐

General physical examination:

1. pulse : /minute
2. B.P: /mm of Hg
3. RR /minute
4. Temprature
5. Pallor ☐ 1- present 2- absent
6. Oedema ☐ 1- present 2- absent
7. Lymphadenopathy ☐ 1- present 2- absent
8. Icterus ☐ 1- present 2- absent
9. Clubbing ☐ 1- present 2- absent
10. Cyanosis ☐ 1- present 2- absent

CVS ☐ 1- normal 2- abnormal if abnormal specify

RS ☐ 1- normal 2- abnormal if abnormal specify

CNS ☐ 1- normal 2- abnormal if abnormal specify

P/A ☐ 1- normal 2- abnormal if abnormal specify

OCULAR EXAMINATION:

	Right eye	**Left eye**
Visual acuity		
1-6/6-6/9 , 2- 6/12- 6/18, 3- 6/24-6/36		
4-6/60, 5- cf 3mt to 1 mt , 6- cfcf to HMCF, 7- PLPR		
1.With Pinhole		
2. With spectacles		
3. Near vision		

(1-n-6 , 2- n-8, 3- n-10 , 4-n-12, 5- n-18, 6- n-36)

Visual axis

Extra ocular movements

Adenexa

1 . Eye lids (1-normal 2- abnormal if 2 specify)

2 . Eye lashes (1-normal 2- abnormal if 2 specify)

3 . Meibomian gland openings (1-normal 2- abnormal if 2 specify)

4 . Lacrimal puncta (1-normal 2- abnormal if 2 specify)

Conjunctiva (1- normal 2- dull 3 -congested)

Cornea

1. surface (1-normal 2- abnormal if abnormal specify)

2. sheen (1-normal 2-dull)

3. sensation (1-normal 2- reduced)

Sclera (1-normal 2- abnormal if abnormal specify)

Anterior chamber (1-normal 2-shallow 3- deep)

Iris (1-normal 2- abnormal if abnormal specify)

Pupil ☐ ☐ (1-normal 2- abnormal if abnormal specify)

Lens ☐ ☐ (1-normal 2-cataractous)

FUNDUS

INVESTIGATIONS

	Right eye	Left eye
1) Schirmers test		
2) Tear film break up time		
3) Rose Bengal test		
4) Impression cytology		

DIAGNOSIS

0 - No dry eye

1 - Mild dry eye

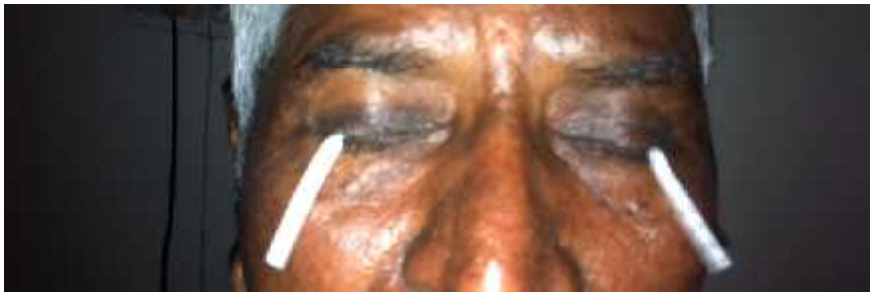
2 - Moderate dry eye

3 - Severe dry eye

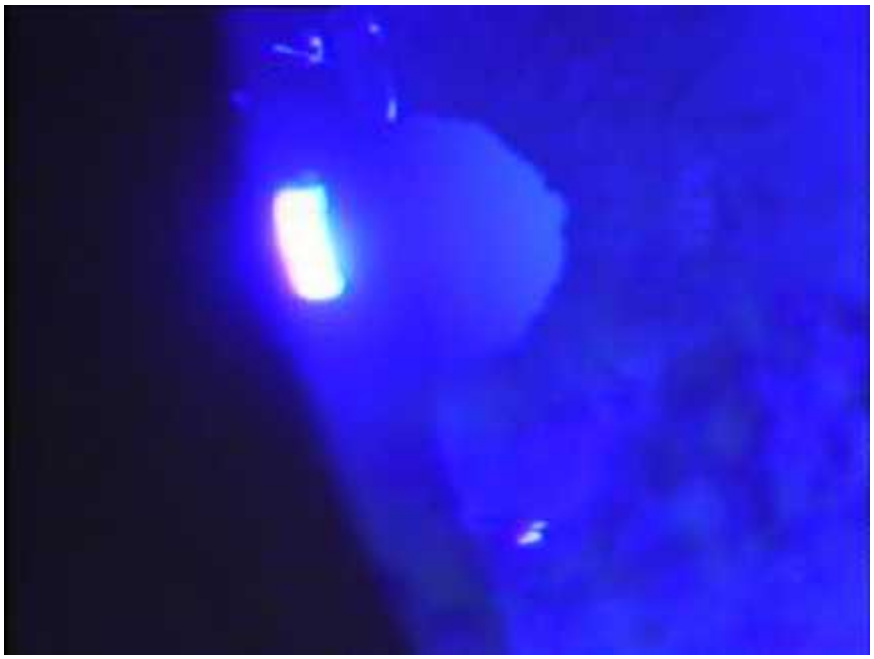
Annexures

Annexure III

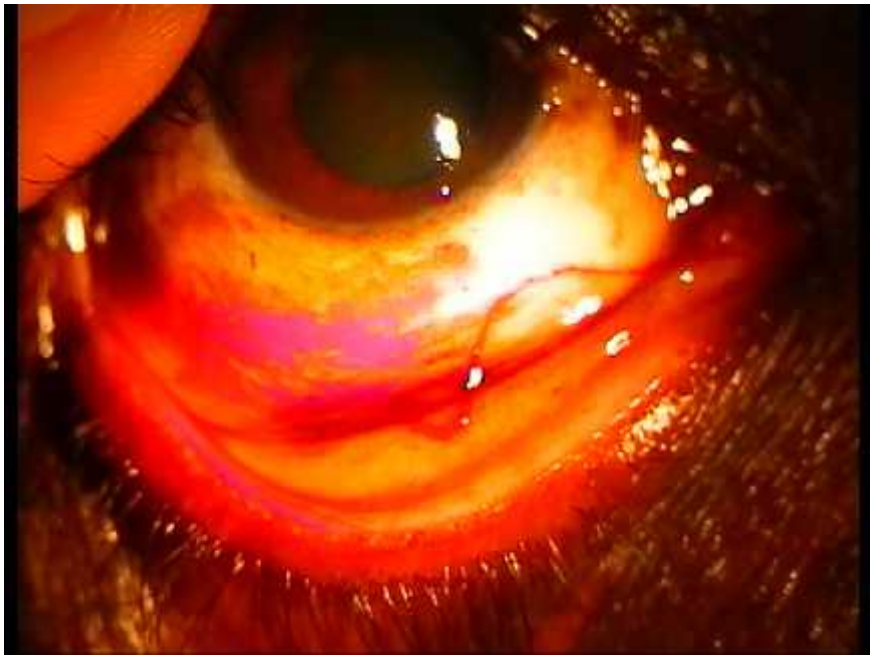
ANNEXURE III – PHOTOGRAPHS



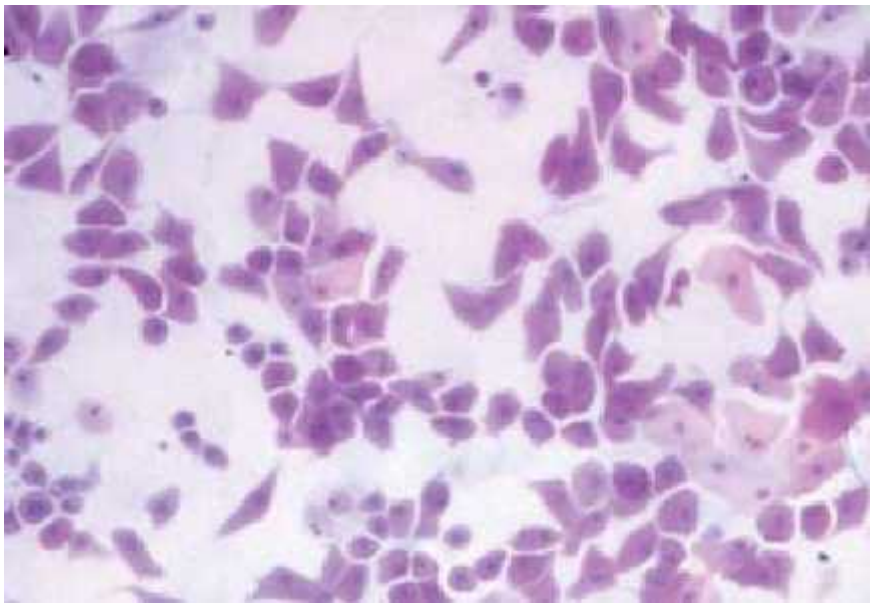
Photograph 1. Schirmer's test



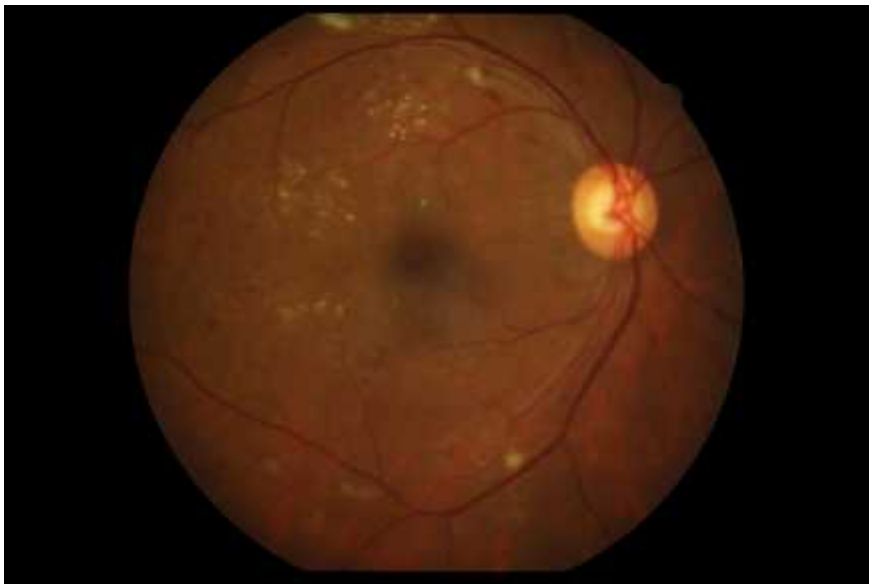
Photograph 2. Dark spot in tear film break up time assessment



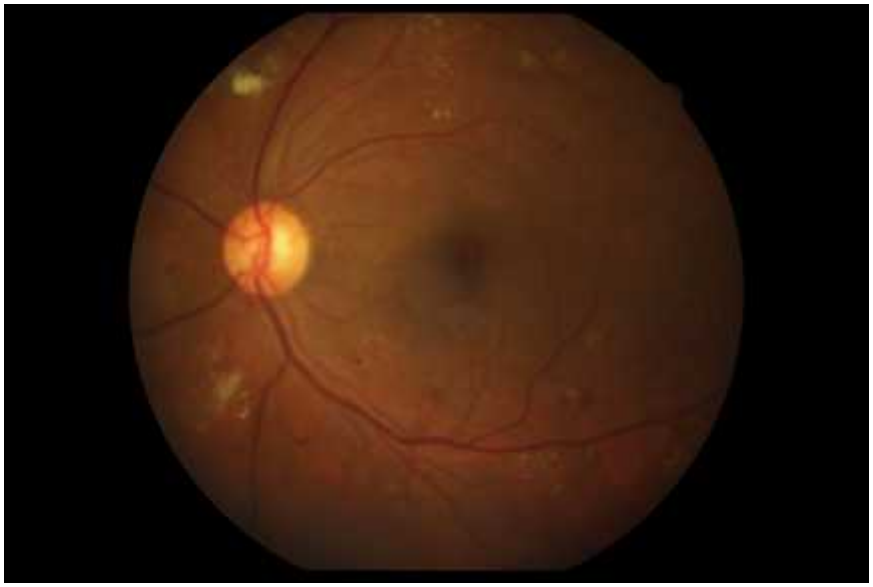
Photograph 3. Rose Bengal staining of conjunctiva



Photograph 4. Grade 2 according to Nelson's grading of conjunctival impression cytology



Photograph 5. Moderate NPDR



Photograph 6. Moderate NPDR

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		Impression cytology
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation								
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	
1	1493462	M	55	2	N	N	N	N	N	N	N	5	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	16	13	20	15	0	0	1
2	401038	M	44	1	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	25	25	15	20	1	1	1
3	1671784	M	52	30	N	N	N	R	R	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	6	5	8	4	3	2	3
4	961619	M	70	8	N	N	N	N	N	N	N	2	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	6	7	5	15	1	1	2
5	60777	F	56	12	N	N	N	N	N	N	N	3	3	NR	NR	BT	BT	G2	G2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	4	2	15	15	1	2	2
6	1420536	M	52	4	N	N	R	R	N	N	N	2	1	NR	NR	BT	BT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	19	13	14	0	0	2
7	1365809	M	54	5	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	10	10	12	14	0	0	1
8	1521433	F	47	1	N	R	S	N	N	N	N	6	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	HM	HM	12	10	14	12	0	0	2
9	617734	M	55	12	N	N	N	R	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	4	3	6	8	0	0	2
10	408286	M	58	10	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	9	3	8	8	4	4	2
11	1370832	M	44	1	N	N	N	R	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	18	25	15	12	0	0	1
12	409422	M	57	10	N	N	N	N	N	R	R	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	6	8	6	8	3	4	3
13	1596137	M	70	6	N	N	N	S	N	S	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	4	7	6	4	0	1	3
14	1630076	M	64	1	N	S	S	S	S	N	R	2	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	2	3	2	4	1	1	2
15	1278038	M	42	2	N	R	S	R	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	10	15	15	2	1	2
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19	1652925	M	69	10	N	N	N	N	N	N	N	2	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	7	3	7	8	4	4	2
20	1426588	M	66	19	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	4	7	7	10	4	3	2
21	873806	M	62	10	S	S	O	N	S	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	9	16	8	10	3	3	0

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation									
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Impression cytology
22	485951	M	56	4	N	N	N	N	S	R	N	1	1	NR	NR	NR	NR	NR	NR	ST	ST	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	14	18	12	15	2	1	0
23	484237	M	45	2	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	18	20	14	18	1	0	1
24	167882	M	66	5	N	N	N	A	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	19	12	12	14	0	0	0
25	420013	M	55	3	S	S	O	N	N	R	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	SNPDR	SNPDR	15	20	14	12	0	3	2
26	433922	M	42	1	N	N	N	N	N	N	N	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	6	14	12	0	0	0
27	420613	M	55	3	N	N	N	N	N	N	N	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	12	14	13	14	0	0	0
28	1689712	F	66	20	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	15	4	8	5	4	4	0
29	1684906	M	62	5	N	N	N	N	N	N	N	4	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	VSNPDR	VSNPDR	15	20	10	12	3	3	1
30	1692307	M	46	1	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	12	16	12	8	2	1	1
31	483002	M	66	10	N	N	N	R	R	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	8	5	10	8	4	3	1
32	478278	M	45	3	N	N	N	N	N	N	N	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	12	16	13	12	1	0	0
33	1701230	M	44	2	N	N	S	N	S	S	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	6	6	10	14	3	1	1
34	1701431	M	61	10	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	3	2	3	4	0	3	2
35	484742	M	57	15	N	N	N	N	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	5	3	10	10	2	3	2
36	479912	F	55	6	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	PDR	PDR	12	14	12	15	2	1	1
37	2176274	M	52	15	N	N	N	R	R	N	N	2	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	PDR	PDR	6	8	10	6	3	4	2
38	1701841	M	71	5	N	N	N	N	N	N	N	1	2	NR	NR	NR	NR	G2	G2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	18	7	12	11	0	1	0
39	486473	F	49	1	N	N	N	N	N	O	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	1	1	12	13	3	1	1
40	420787	M	50	1	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	8	2	12	13	2	2	1
41	1695373	M	65	5	N	N	R	N	R	R	N	2	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	1	1	15	13	2	3	0
42	1692893	M	67	5	N	N	N	R	N	N	N	3	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	15	25	13	10	0	2	0

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		Impression cytology
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation								
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	
43	1186620	F	44	21	O	N	S	O	O	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	9	1	10	8	2	4	2
44	420829	F	49	1	R	N	R	R	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	1	4	10	13	0	0	0
45	1171630	M	53	3	N	N	N	N	N	N	N	3	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	20	15	10	12	0	1	1
46	170294	M	47	1	N	N	N	N	N	N	N	4	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	2	1	3	5	3	3	1
47	480433	M	41	2	N	N	S	R	R	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	PDR	PDR	12	15	12	16	2	1	1
48	2054763	M	46	5	N	N	N	N	N	N	N	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	17	10	9	1	0	0
49	584353	F	48	10	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	2	6	7	10	3	2	2
50	1042434	F	65	1	N	N	N	N	N	N	N	2	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	6	16	7	10	2	0	1
51	1689624	F	49	2	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	15	30	10	12	0	0	1
52	671120	F	68	1	N	N	N	N	N	N	N	5	5	NR	NR	BT	BT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	18	25	10	14	0	1	1
53	1815420	F	56	1	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	17	20	10	10	0	0	0
54	429512	M	63	18	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	10	10	11	13	0	0	2
55	442725	M	69	7	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	20	18	10	12	3	4	2
56	1427240	F	58	20	N	N	N	S	N	N	N	5	4	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	4	1	4	3	3	4	2
57	1370579	M	40	1	N	N	N	N	N	N	N	1	3	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	15	25	10	13	1	2	1
58	2185727	M	48	2	N	N	A	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	18	20	12	10	1	0	0
59	1778873	M	50	8	N	N	N	S	N	N	N	1	1	NR	NR	BT	BT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	8	17	7	8	2	3	1
60	1779226	F	51	3	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	12	13	14	12	2	1	1
61	2160513	M	55	2	N	N	N	N	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	15	17	14	1	1	0
62	2192648	M	66	4	N	N	N	R	S	N	N	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	18	12	10	0	1	0
63	2192648	M	67	27	N	N	N	N	N	N	N	3	3	NR	NR	BT	BT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	8	6	10	6	2	4	2

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation								
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Impression cytology
64	436064	M	43	12	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	8	8	6	8	2	1	1
65	434957	M	51	16	N	N	S	S	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	4	10	4	5	0	0	2
66	1283354	M	70	1	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	12	16	13	11	0	1	1
67	1704291	M	47	3	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	18	12	14	2	2	0
68	1791802	M	42	12	N	N	N	O	S	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	1	1	4	6	3	2	1
69	433738	M	60	3	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	NDR	NDR	1	1	1	1	2	2	1
70	60777	F	56	10	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	17	13	17	1	2	1
71	1837218	M	63	8	N	N	N	N	N	N	N	1	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	1	1	6	6	3	4	2
72	1721622	M	40	9	R	N	O	N	O	N	N	1	1	NR	NR	BT	BT	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	16	8	6	4	4	4	1
73	1802062	M	60	2	N	N	N	N	N	N	N	4	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	16	20	4	5	3	3	1
74	1802161	F	55	4	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	10	25	10	13	0	0	1
75	1722611	M	63	25	N	N	N	S	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	SNPDR	SNPDR	8	5	5	8	4	5	2
76	2174232	F	45	2	N	N	N	N	N	N	N	3	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	14	16	12	15	2	1	0
77	2184131	M	42	6	N	N	N	R	R	O	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	8	6	6	4	5	6	2
78	436781	M	47	5	N	N	N	N	N	O	R	4	4	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	HM	HM	12	15	12	9	2	1	1
79	439547	M	50	12	N	N	N	N	N	N	N	1	2	NR	NR	BT	BT	NR	NR	NR	NR	CG	CG	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	10	8	9	6	4	5	2
80	501837	F	74	10	N	N	N	N	N	N	N	3	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	HM	12	7	10	5	0	0	2
81	439854	M	44	3	R	R	O	N	O	O	R	2	2	NR	NR	NR	NR	NR	NR	NR	NR	CG	CG	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	11	16	7	5	2	2	0
82	1808740	F	65	5	N	N	N	N	N	N	N	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	27	15	10	15	2	2	1
83	46321	M	73	1	N	N	N	N	N	N	N	2	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	16	10	8	2	2	0
84	1043863	M	72	20	N	N	R	N	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	2	1	4	3	2	2	2

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		Impression cytology
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation								
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	
85	180900	M	61	1	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	10	16	10	10	1	2	0
86	444852	M	65	1	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	30	30	2	4	1	2	1
87	180900	M	61	1	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	15	13	13	15	2	2	1
88	1840291	M	48	2	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	CG	CG	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	6	8	5	8	2	3	2
89	439034	M	50	7	N	N	S	N	R	N	N	7	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	HM	NDR	20	20	5	7	0	0	1
90	190800	M	56	17	N	N	N	N	N	N	N	6	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	PDR	PDR	8	8	4	6	4	4	2
91	987495	F	70	2	N	N	S	N	N	N	N	4	6	NR	NR	BT	BT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	HM	15	15	5	7	0	0	1
92	1868432	M	70	1	N	N	R	R	N	N	N	3	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	15	15	2	4	2	1	1
93	1879466	F	58	8	N	N	N	N	N	N	N	5	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	HM	11	5	10	7	3	3	0
94	1852326	M	58	3	N	N	N	N	N	N	N	3	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	10	10	10	12	0	1	1
95	584193	F	60	15	R	N	R	R	N	N	N	5	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	2	1	4	3	4	4	2
96	1858386	F	48	9	R	N	R	R	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	3	3	6	4	3	4	2
97	1862203	M	41	1	R	R	R	R	N	N	N	2	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	18	10	10	0	0	1
98	1862036	M	52	2	N	S	R	O	O	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	15	20	7	6	1	1	1
99	1042338	M	58	15	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	1	1	4	6	3	3	3
100	1317015	F	63	1	N	N	R	R	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	10	20	10	10	2	3	1
101	1876374	M	56	15	N	N	S	R	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	10	14	10	10	4	5	3
102	1466554	M	58	1	N	N	N	R	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	16	20	10	10	3	2	1
103	1687741	M	61	7	N	N	N	S	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	8	11	7	8	4	5	3
104	1682036	F	65	7	N	N	N	S	S	N	N	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	SPK	NR	NR	NDR	NDR	5	7	6	7	3	3	0
105	609976	M	56	19	N	N	N	N	N	N	N	2	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	VSNPDR	VSNPDR	4	6	8	5	4	4	2

MASTER CHART

Serial number	In patient Number	Sex	Age (Years)	Duration of Diabetes (Years)	Dry Eye Questionnaire							Ocular examination																				Investigations						
												Visual acuity		Adnexa								Conjunctiva		Cornea						Fundus		Schrimers test		Tear file breaku		Rose bengal test		
														Eye lids		Eye lashes		Meiobian gland opening		lacrima puncta				Surface		Sheen		Sensation									
					Dryness	gritty sensation	Burning sensation	watering	Redness	crusting on the eyelashes	Sticking of the eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eyes	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Impression cytology
106	1900389	M	55	4	N	N	N	N	N	N	N	3	2	NR	NR	NR	NR	NR	NR	NR	NR	DL	DL	NR	NR	NR	NR	NR	NR	MDNPDR	MDNPDR	30	30	10	10	0	1	1
107	1892052	M	52	5	R	N	S	N	N	N	N	4	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	SPK	NR	NR	NR	NR	NR	PDR	PDR	9	7	10	10	1	1	1
108	684992	M	60	16	N	N	N	N	N	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	CG	CG	NR	SPK	NR	NR	NR	NR	NDR	NDR	8	10	1	1	2	2	2
109	1792592	M	47	6	N	R	R	S	N	N	N	3	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	10	4	5	0	4	2
110	1784607	M	45	4	N	N	N	N	S	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	10	20	10	14	2	1	1
111	684992	M	60	15	N	N	S	R	N	N	N	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	5	7	5	8	5	5	2
112	1903089	M	50	3	R	N	N	N	R	N	N	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	14	18	10	15	2	0	0
113	1605419	M	60	2	N	N	N	N	N	N	N	2	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	MNPDR	MNPDR	13	5	10	10	0	1	1
114	1846105	M	63	24	N	N	N	N	N	N	N	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	8	15	6	4	6	4	3
115	1358886	M	59	15	N	N	R	R	N	N	N	3	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	4	8	8	10	2	0	1
116	484298	M	49	1	N	N	N	N	N	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	13	18	12	10	1	1	1
117	1775970	F	40	14	N	N	N	R	R	N	N	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NDR	NDR	18	14	14	12	3	2	2

MASTER CHART

Diagnosis
N
N
Y
Y
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MASTER CHART

Diagnosis
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MASTER CHART

Diagnosis
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MASTER CHART

Diagnosis
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MASTER CHART

Diagnosis
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MASTER CHART

Diagnosis
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Y

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART

1	- 6/6 to 6/9
2	- 6/12 to 6/18
3	- 6/24 to 6/36
4	- 6/60
5	- Counting finger 3 meters to 1 meter
6	- Counting finger close to face to hands movement close to face
7	- Perception of light and projection of rays
A	- All the time
BT	- Blepharitis
CG	- Congested
DL	- Dull
F	- Female
G1	- Grade 1
G2	- Grade 2
G3	- Grade 3
HM	- Hazy media
MDNPDR	- Moderate non proliferative diabetic retinopathy
M	- Male
MNPDR	- Mild non proliferative diabetic retinopathy
NDR	- No diabetic retinopathy
N	- Never
NR	- Normal
O	- Often

PDR	- Proliferative diabetic retinopathy
R	- Rarely
SNPDR	- Severe non proliferative diabetic retinopathy
SPK	- Superficial punctate keratitis
S	- Sometimes
ST	- Stenosed
VSNPDR	- Very severe non proliferative diabetic retinopathy