CHAPTER 4:
OCULAR SURFACE DISORDERS IN DIABETES

1. DRY EYE IN DIABETES

Diabetes is a leading cause of ocular morbidity which is progressive and preventable with early diagnosis and treatment. In both the developed and developing countries It is a major cause of avoidable blindness. Ocular complications of diabetes mellitus include diabetic retinopathy, cataract, glaucoma, and ocular surface disease among others. Duration of diabetes, glycemic control, coexisting hypertension, hyperlipidemia, nephropathy and anaemia have proven to a play role in the progression of diabetes and its complications.

Recently ocular surface problems especially dry eye has drawn attention in diabetic patients. Diabetes and dry eye appear to have a significant impact on the quality of life of patients in several studies.

Dry eye was earlier termed a complex disorder of the tear film and ocular surface as a result of tear deficiency or excessive tear evaporation. Damage to interpalpebral ocular surface occurs, with a variety of symptoms such as ocular discomfort and visual disturbance among others . Dry eye syndrome (DES), is a multifactorial disorder due to inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency and meibomian gland dysfunction. Grittiness, burning sensation, foreign body sensation, photophobia, redness and blurred vision are some of the symptoms of patients with dry eye. The micro vasculopathy and autonomic neuropathy in long term diabetics can lead to absence of these symptoms but presents with clinical signs of dry eye. According to Tear film ocular society (TFOS) dry eye workshop 2 Patients with dry eye can have serious corneal complications such as, superficial punctuate keratitis, neurotrophic keratopathy and persistent epithelial defect.

According to DEWS conducted in the year 2017, dry eye was defined as a multifactorial disease of ocular surface characterized

by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation and neurosensory abnormalities play a major role in etiology. Dry eye can beclassified into 2 types as tear-deficient and evaporative. Similarly, in diabetes, dry eye may be tear deficient or evaporative.

The tear film consists of 3 layers, outer lipid layer (secreted by meibomian glands), middle aqueous layer (secreted by the lacrimal gland) and inner mucin layer (secreted by goblet cells of conjunctiva). The ocular surface comprises of the cornea, conjunctiva and also includes the lacrimal gland, meibomian gland, lids, with the sensory and motor nerves that connect them.

Quantitative and qualitative abnormalities in tear secretion, alteration of epithelial barrier leading to poor adhesion of regenerating epithelial cells, autonomic neuropathy causing decreased corneal sensitivity lead to tear film and ocular surface changes in diabetes causes dry eye which can affects the quality of life of an individual. There is no gold standard diagnostic test for dry eye disease hence a combination of signs and symptoms is commonly used as the basis for diagnosis. Several studies have been conducted to study dry eye, its risk factors, tear film parameters, ocular surface irregularities, prevalence and the various methods to diagnose dry eye. Examination of diabetic patients for dry eye should be an integral part of assessment of diabetic eye disease along with evaluation of diabetic retinopathy.

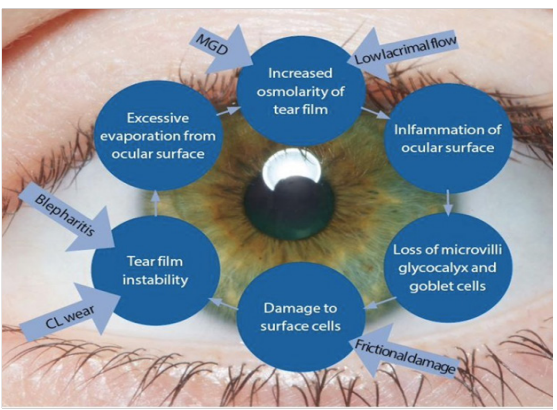

Image: Vicious cycle of tear film and ocular surface disorder

Pathophysiology of dry eye:

DM can lead to DES (DRY EYE SYNDROME) through a variety of mechanisms, but the association between DM and DES is unclear. Extensive hyperglycemia is the most possible mechanism responsible for dry eye in DM which causes corneal neuropathy. Corneal neuropathy inturn leads to tear film instability and lower tear film break up time (TBUT) values due to conjunctival goblet cell loss. Mucin, which forms the mucin layer of the tear film covers the villus surface of the corneal epithelium and reduces evaporative tear loss is produced by conjunctival goblet cells. The other suggested mechanisms for disruption ofcorneal integrity include AGE accumulation and polyol pathway bi-product accumulation within the corneal layers. It is believed that DM affects tear production and quality by compromising the functional integrity of the lacrimal gland as well. Corneal sensitivity is also reduced in DM, which affects the stimulation of basal tear production. Both lacrimal gland integrity and corneal sensitivity are shown to be affected by diabetic neuropathy. These proposed mechanisms imply that DM affects both tear production and corneal integrity, suggesting disruption to one or both may cause and lead to the exacerbation of DES.

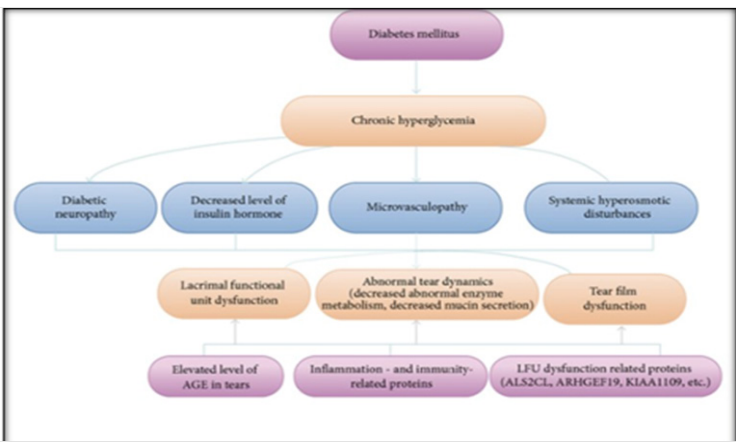

Image: showing pathophysiology of dry eye.

Tests to evaluate dry eye:

1. Ocular symptoms:

- Grittiness
- Foreign body sensation
- Burning
- Irritation
- Stinging
- Watering
- Photophobia
- Diminution of vision
- Blurring of vision
- Redness
- Dryness

Presence of symptoms is graded as follows

- Less than 2 symptoms: normal
- More than 2 symptoms: abnormal

2. Schirmer test without anaesthesia:

Whatman filter paper no 41 is used to perform the Schirmer test. The patient is asked to look up and the strip is placed in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. The patient is asked to sit with eyes gently closed for 5 minutes and the distance of the strip wetted is measured in millimetre and reading of 10 or lesser is considered abnormal. A scoring was given to each patient based on the millimetre of Schirmer strip wetting as follows

- 0 to 5 mm – Grade 1, abnormal
- 6 to 10 mm – Grade 2, abnormal
- 11 to 15 mm – Grade 3, normal

- More than 15 mm – Grade 4, normal

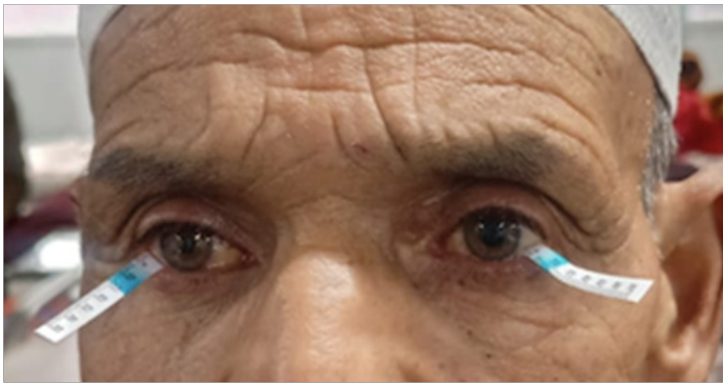

Image: showing schirmer test being done

3. Tear meniscus height (TMH):

1% fluorescein dye strip is used to stain the tear film and to measure the tear film meniscus height. Precorneal tear film is stained by placing the strip in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. The patient is placed in front of the slit lamp and using the cobalt blue filter, height of the fluorescent stained meniscus is measured with a scale in millimetre. Graded as follows:

- Less than 1mm–abnormal
- More than 1mm-normal

4. TBUT – tear film breakup time:

With the dye stained pre corneal tear film, the patient is asked to blink few times then seated on a slit lamp and viewed under cobalt blue filter. The time taken to visualize the first dry spot on the cornea is noted with a stopwatch. Reading of 10 or lesser seconds is abnormal.

Graded as follows:

- Less than 10 seconds – abnormal

- More than 10 seconds – normal

5. Corneal staining with fluorescein

It is scored using the Oxford system of grading for cornea and conjunctiva which is adapted from corneal and conjunctival staining clinical education, multimedia from American academy of Ophthalmology.

It is graded as follows:

0- absent

1- Minimal

2- Mild

3- Moderate

4- Severe

5- Very Severe

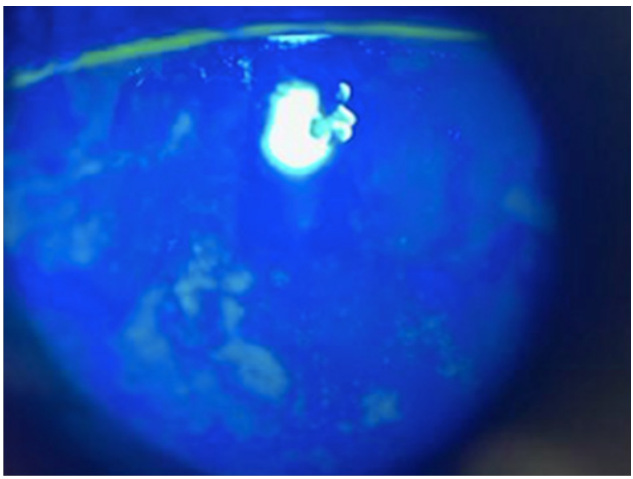

Image: showing corneal fluorescein staining positive in a dry eye patient

Score of 3 or more is abnormal as was considered as corneal staining positive.

- Corneal stain positive – abnormal

- Corneal stain negative – normal

PANEL	GRADE	CRITERIA
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Image: showing grades of corneal staining in dry eye (ref AAO)

6. Conjunctival staining:

Lissamine green is used to stain the conjunctiva to look for dead and degenerated cells. Conjunctiva is stained with the strip after 5 minutes of the previous fluorescein staining and done by placing the lissamine green strip in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. Patient is placed in front of the slit lamp and using the red free filter, the extent of conjunctival staining both temporal and nasal conjunctiva was graded using the Oxford system of grading for cornea and conjunctiva.

0- absent.

1- minimal.

2- mild.

3- moderate.

4- marked.

5- severe.

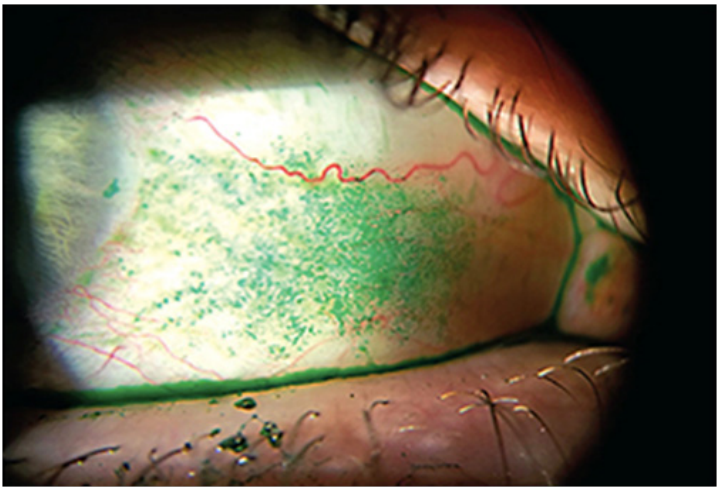

Image: showing conjunctival stain positive with lissamine green stain.

Score of 3 or more is abnormal.

- Conjunctival stain positive – abnormal
- Conjunctival stain negative - normal

7. Presence of strands / filaments:

Presence of strands / filaments is noted as positive or negative by viewing with the slit lamp after fluorescein staining.

- Strands/ filaments present – abnormal
- Strands/ filaments absent – normal More than 3 positive tests : dry eye disease

Duration of diabetes also plays a major role in development of dry eye disease, so patients having diabetes for longer durations

have more chance of having dry eye than recently diagnosed patients. Besides duration status of retinopathy also plays a role in dry eye.

Patients with diabetic retinopathy usually have worse scores on tear film tests and ocular surface analysis compared to patients without retinopathy which suggests poor glycemic control is also an important factor in causing dry eye.

The first and very important step in the diagnosis of dry eye is symptom assessment, dry eye is believed to be a 'symptom based' disease. So the first test in dry eye is evaluating the ocular symptoms of the patient. proper history taking thus takes a very important role is guiding us towards dry eye diagnosis.

1. Therapy:

DES may cause loss of vision, scarring, perforation, and corneal infection among other complications. If patients with dry eye are treated in time, it will prevent complications ofDES. The patients of DES are treated with tear supplements called "artificial tears" which contains surfactants, different viscosity agents and electrolytes.

Dry eye disease is the outcome of various factors resulting in inflammation of the cornea and conjunctiva. Artificial tears can reduce blurred vision, and the symptoms of dry eye, temporarily. These agents do not contain the cytokines and growth factors which are comprised in normal tears and do not have direct anti-inflammatory effect so Anti- inflammatory drugs are also widely used for the treatment of DES. The most widely used anti-inflammatory agents are topical corticosteroids, NSAID, and cyclosporine.

Correlation of dry eye with other modalities of evaluation of tear film and ocular surface such as tear osmolarity and conjunctival impression cytology have proven to be better markers in studies. Thus the progression of dry eye is multifactorial. If untreated it causes serious ocular complications and much distress to the patient. Thereby early identification of symptoms, signs and timely evaluation by the treating Ophthalmologist, must be

given priority in the analysis for dry eye in diabetic patients.

2. Diabetic keratopathy:

DM can trigger acceleration of ocular surface abnormalities which have been termed diabetic keratopathy. Patients with diabetes in contrast to healthy persons, have corneal epithelial erosions that may recur and be associated with unresponsiveness to conventional treatment regimens. This clinical condition is known as diabetic keratopathy. Diabetic keratopathy includes various symptomatic corneal conditions, such as, punctate keratopathy and persistent corneal epithelial defect.

Diabetic keratopathy is a common complication of patients with evidence of DR. A study reported that several symptomatic corneal epithelial lesions usually occur in diabetic patients at the rate of 47% to 64%. Other study showed that the incidence of diabetic keratopathy in diabetic patients with DR was 2 times greater than that of patients without DR. Several studies reported that the incidence of diabetic keratopathy increased following pars planavitrectomy, penetrating keratoplasty, laser iridectomy, and refractive surgery in diabetic patients.

Pathogenesis:

Several pathophysiological abnormalities have been shown in diabetic keratopathy which are an abnormally thickened and discontinuous basement membrane, abnormal adhesion between the stroma and basement membrane, increased epithelial fragility, decreased epithelial healing rates, increased sorbitol concentrations, decreased oxygen consumption and up-take, increase in the polyol metabolism, decreased or alter epithelial hemidesmosomes, and increased glycosyl transferase activity.

Recently, studies have demonstrated that there is a relationship between AGE and development of diabetic keratopathy as well. Increased AGE in the laminin of the corneal epithelial basement membrane causes abnormaly weak attachment between the basal cells and basement membrane of the cornea in diabetics. Also, the loss of the corneal sensation and neural stimulus have been regarded as the reason of the development of diabetic

keratopathy. Axonal degeneration of corneal unmyelinated nerves occurs under chronic hyperglycemic conditions.

Clinical evaluation:

Diabetic keratopathy is a condition that should be closely monitored because it can result in blindness . Early diagnosis and treatment of diabetic keratopathy, particularly, before corneal complications occur, is very essential. If the diagnosis is late, patients will become resistant to the routine treatment of corneal defects. Nonhealing corneal epithelial erosion may also occur after pars plana vitrectomy for advanced PDR. If corneal epithelium is removed manually for clarity by surgeons, this conditions may accelerate dramatically. So, when diabetic patients are examined after vitrectomy their corneas should be examined carefully.

Therapy:

Keratopathy is generally treated with artificial tears, and antibiotics. Additionally, bandage contact lens, and tarsorrhaphy have been used for re-epithelialization. In selected cases newtreatments modalities will be used such as, topical administration of naltrexone, nicergoline, aldose reductase inhibitor and some growth hormones to accelerate re-epithelialization. All of these drugs were associated with a high corneal epithelial wound healing rate.

Recently, new topical drugs such as substance P and IGF-1 were tested on diabetic animals to accelerate re-epithelialization. Successful outcomes were obtained with these new drugs.

Corneal epithelial barrier function was improved by topical aldose reductase inhibitors, but superficial punctate keratopathy could not be prevented by these topical drugs.

Aminoguanidine had beneficial effects in corneal epithelial defects, by improving attachment between the epithelial cells and basement membrane of the cornea. The in vivo beneficial effect of amino-guanidine were unknown. In additional to these new drugs, amniotic membrane transplantation is used to treat persistent corneal epithelial defects and can provide relief to the

patient.

Conclusion:

DM and its ocular complications remain a major cause of blindness despite increased understanding of these ocular conditions and identification of successful treatments because early diagnosis is not done. Timely diagnoses and therapy can prevent all the complications of diabetes. Therefore, periodic eye examinations are required for the reduction of diabetes- related vision loss. Good blood glucose control and other systemic risk factors such as hypertension, and hyperlipidemia are main goal to prevention of ocular complications of DM.

References

1. Li WC, Kuszak JR, Dunn K, Wang RR, Ma W, Wang GM, Spector A, Leib M, Cotliar AM, Weiss M. Lens epithelial cell apoptosis appears to be a common cellular basis for non-congenital cataract development in humans and animals. J Cell Biol. 1995;130:169–181. [PMC free article] [PubMed] [Google Scholar]

2. Papadimitriou DT, Bothou C, Skarmoutsos F, Alexandrides TK, Papaevangelou V, Papadimitriou A. The autoimmune hypothesis for acute bilateral cataract in type 1 diabetes. Diabetes Metab. 2016;42:386–387.[PubMed] [Google Scholar]

3. Sayin N, Kara N, Pekel G. Ocular complications of diabetes mellitus. World J Diabetes. 2015; 6(1):92–108. doi:10.4239/ wjdv6.i1.92.

4. Jain S: Dry Eyes in Diabetics. Diabetes Care 1998,21(8):1364- 1382.

5. Saini JS, Khandalavla B. Corneal epithelial fragility in diabetes mellitus. Can J Ophthalmol 1995; 30:142-6.

6. Harrison TR: Diabetes Mellitus. In Harrison Principle of Internal Medicine 15th limited edition. Edited by: Branwald E, Fauci S, Kasper D, USA, Mc Grow-Hill; 2001:2121.

7. Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). Ocul Surf 2007; 5:75-92 [PMID: 17508116].

8. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. Lemp MA CLAO J. 1995 Oct; 21(4):221-32.

9. Nielsen NV, Lund FS. Diabetic polyneuropathy, corneal sensitivity, vibratory perception and Achilles tendon reflex in diabetes. ActaNeurologicaScadinavica

1979, 59:15–22.

10. Dews TFOS DEWS II Definition and Classification Report, Jennifer P. Craig, Kelly

12. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology 2001; 108:586-92.

13. Goebbels M. Tear secretion and tear film function in insulin dependent diabetics. Br J Ophthalmology 2000; 84:19-21.

14. YoonKC,ImSK,SeoMS.Changesoftearfilmandocularsurface in diabetes mellitus. Korean J Ophthalmology 2004; 18:168-74.

15. Inoue K, Kato S, Ohara C, Numaga J, Amano S, Oshika T. Ocular and systemic factors relevant to diabetic keratoepitheliopathy. Cornea 2001; 20:798-801.

16. Chous P. Dry Eyes and Diabetes Often Go Hand in Hand: dLife Blog. Connecticut: LifeMed Media, Inc.; 2013. Available from: http: // www.dlife.com/ diabetes/complications/eye-care/chous_sept 2006 [Last cited on 2015 Oct 02].

17. Kesarwani D, Rizvi SW, Khan AA, Amitava AK. Vasenwala SM, Siddiqui Z. Tear film and ocular surface dysfunction in diabetes mellitus in an Indian population. Indian J Ophthalmol2017;65:301-4.

18. ShamsheerRPandArunachalamC:Aclinicalstudyofmeibomian gland dysfunction in patients with diabetes. Middle East African Journal of Ophthalmology 2015; 22: 462– 466.

19. Shih KC, Lam KSL and Tong L: A systematic review on the impact of diabetes mellitus on the ocular surface. Nutrition and Diabetes 2017; 7: e251.

20. Sahai A, Malik P. Dry Eye: Prevalence and Attributable Risk Factors in a Hospital- Based Population. Indian J Ophthalmol 2005; 53:87-91.

21. Manaviat, Masoud Reza et al. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. BMC ophthalmology vol. 8 10. 2 Jun. 2008, doi:10.1186/1471-2415-8-10.

22. ZhangX,ZhaoL,DengS,SunX,WangN.DryEyeSyndromein Patients with Diabetes Mellitus: Prevalence, Etiology, and Clinical Characteristics. J Ophthalmol. 2016; 2016:8201053. doi:10.1155/ 2016/8201053.

23. Y. Xu. Prevalence and control of diabetes in Chinese adults. The Journal of the American Medical Association, vol. 310, no. 9, pp. 948–959, 2013.

24. NGupta,IPrasad,RJainandPD'SouzaEstimatingtheprevalence of dry eye among Indian patients attending a tertiary ophthalmology clinic. Annals of Tropical Medicine and Parasitology, Vol. 104, No 3, 247-255(2010).

25. K. Kalaivani Diabetes and dry eye, International Journal of Ocular Oncology and Oculoplasty, January-March, 2017; 3(1):40-42.

26. V Ramalakshmi, S Hariramasubramanian, A Rajalakshmi, Heber Anandan. Incidence of Dry Eye Syndrome in Patients with Type II Diabetes Mellitus. International Journal of Scientific Study, March 2017, Vol 4, Issue 12.