



COMPARATIVE STUDY OF DRY EYE IN DIABETIC AND NON DIABETIC PATIENTS IN TERTIARY CARE CENTRE OF KUMAON REGION OF UTTARAKHAND

Dr. Deepti Joshi¹, Dr. Shanti Pandey², Dr. Vivekanand Satyawali³, Dr. G. S. Titiyal⁴

¹Post graduate 3rd year, Department of Ophthalmology, Government Medical College, Haldwani, Nainital, Uttarakhand

²Associate Professor, Department of Ophthalmology, Government Medical College, Haldwani, Nainital, Uttarakhand

³Associate Professor, Department of Medicine, Government Medical College, Haldwani, Nainital, Uttarakhand

⁴Professor, Department of Ophthalmology, Government Medical College, Haldwani, Nainital, Uttarakhand

Conflicts of Interest: Nil

INTRODUCTION

Type II diabetes mellitus is a major public health concern in this modern day. It is perhaps the most important non-infective epidemic to hit the globe in the present millennium. There are 425 million people with diabetes in the World. There will be 629 million people with diabetes in the World in 2045. Diabetes is fast gaining the status of a potential epidemic in India with more than 72 million diabetic individuals currently diagnosed with the disease¹.

Diabetes impacts almost all structures of the eye including eyelids, extra-ocular muscles, tear-film, cornea, iris, cranial nerves, and retina.²

Diabetic retinopathy and cataract are well known complication of diabetes but recently attention has been drawn to ocular surface problems especially dry eye in diabetics³. Diabetic keratopathy can induce quantitative and qualitative abnormalities in tear secretion, contributing to poor corneal sensitivity and poor adhesion of regenerative epithelial cells³. Most of the dry eye associated with diabetes is as a result of insufficient tear production due to autonomic neuropathy of lacrimal gland⁴. While diabetic retinopathy (DR) and diabetic cataracts are well-

known complications, dry eye syndrome (DES), also referred to as keratoconjunctivitis sicca, is also common in the diabetic population. Studies have indicated 54% prevalence of asymptomatic and symptomatic DES, in diabetes⁵. The cornea is one of the most compactly innervated parts of the human body containing myelinated A- δ and unmyelinated C fibers, deriving its innervation from the ophthalmic division of the trigeminal nerve. Recent data suggested that patients with peripheral neuropathy have corneal nerve fiber damage and decreased corneal sensitivity⁶. According to the International Dry Eye Workshop (DEWS), the reduced corneal sensitivity favours the occurrence of DES in two ways: first by decreasing the reflex-induced lacrimal secretion and second by reducing the blink rate and increasing evaporative tear loss⁷. Dry eye (DE) is a multifactorial pathology characterized by a progressive dysfunction of the lacrimal and meibomian glands that typically leads to reduced aqueous tear production and increased tear evaporation, respectively⁸⁻¹⁰. These disorders are associated with signs and symptoms of ocular discomfort such as stinging, eye watering or redness and may cause serious irritation to the inter palpebralocular surface, particularly the cornea.

AIM

This study aimed to compare the dry eye symptoms and tear functions between diabetics and non-diabetics subjects.

PATIENTS AND METHODS

This was case control study carried out in outpatient departments of Ophthalmology at Government Medical College Haldwani.

After taking clearance from ethical committee A total of 200 eyes of 100 patients (GROUP A-50, non diabetic GROUP B-50 type 2diabetic), seeking advice for refractory error were included in study after taking informed consent. Group B further divided into two subgroups diabetic with retinopathy and diabetics without retinopathy.

A diagnosis of diabetes was made if the fasting blood glucose ≥ 126 mg/dl on two separate occasion, or 2 hour post prandial glucose ≥ 200 mg/dl, or random blood sugar ≥ 200 mg/dl with symptoms of diabetes.

Data of all patients including age, sex, duration of diabetes, as well as a history of other diseases were obtained by reviewing medical records and through direct patient interviews. Detailed general physical examination and systemic clinical examination was done for all subjects.

Structures of the eye were assessed with slit-lamp biomicroscopy examination. Retinal status was evaluated by indirect ophthalmoscopy after dilation with tropicamide drop, and diabetic retinopathy was graded according to early Treatment Diabetic Retinopathy Study.

Participants were asked about symptoms suggestive of dry eye like burning, itching, lacrimation, foreign body sensation etc if more than two of these symptoms were present they classified as having symptoms of dry eye.

Dry eye was confirmed by tear film break up time (TBUT) and Schirmer's I test. Diagnosis was established by positivity of one or both the tests (TBUT or Schirmer's test).

Schirmer's test:

Schirmer's test is useful in assessment of aqueous layer deficiency. The test involves measuring the

amount of wetting of special (no.41 Whatman) filter paper, 5 mm wide and 35 mm long.

Schirmer test was performed without topical anesthetic.

The strip was folded at the notch and placed at the junction of the middle and lateral thirds of the lower eyelids and allowed to stay in place for 5min with patient's eyes gently closed.

The filter paper was removed, and the amount of wetting was measured.

More than 10mm of wetting was considered normal, 8–10mm of wetting was considered mild dryness, 5–7 mm of wetting was considered moderate dryness, and less than 5mm of wetting was considered severe dryness.

Tear film break up time:

TBUT is a clinical test used to assess for evaporative dry eye disease and also for aqueous layer deficiency. To measure TBUT, fluorescein is instilled into patient's tear film. The individuals were then instructed to blink several times for a few seconds to ensure adequate mixing of fluorescein. The tear film was examined with a broad beam and a cobalt blue filter and asked not to blink. The interval between the last complete blink and the appearance of the first corneal black spot or line in the stained tear film was measured using a stopwatch.

A TBUT value more than 10s was considered normal, a value of 8–10s was considered mild dryness, a value of 5–7s was considered moderate dryness, and a value less than 5s was considered severe dryness.

In this study, we determined the changes in tear film parameters and ocular surface in a group of type 2 diabetes mellitus patients and compared the results with a non-diabetic control group.

Exclusion criteria

1. Patients using medications such as antihistamines or antidepressants, oral contraceptives, and diuretics or history of chronic ocular drug abuse
2. Ocular surgery in last three months
3. Patients who had undergone LASIK surgery.

4. Patients wearing contact lenses.
5. Patients having Sjogren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and Parkinson’s disease, Mucocutaneous disorder.
6. Patients with known vitamin A deficiency.
7. Pregnant women.

Parameters between groups were analysed by the χ^2 -test, Fisher' exact test.

A *P* value of less than 0.05 was considered statistically significant.

Result

In diabetic group there were 30(60 eyes) female and 20(40 eyes) male patients .In non- diabetic group there were 29(58eyes) female and 21(42 eyes) male patients. The mean age of diabetic patients was 52.46years (SD=9.10 years) and that of the non diabetic group was 49.32 years (SD=9.20 years). The mean duration of DM in the study group was 10.26 years (SD=6.88 ranging from 1.0 to 25.0 years).

There was a statistically significant difference between non diabetics and diabetics regarding age with a *P* value of 0.028, whereas there was no statistically significant difference regarding sex with a *P* value of 1.000(table 1)

Table 1 Comparison of gender and age between diabetic and nondiabetic groups

	NONDIABETICS	DIABETICS	X ²	P VALUE
SEX				
FEMALE EYES	60	58	0.000	1.000
MALE EYES	40	42		
AGE				
MEAN±SD	49.32±9.20	52.46±9.10	2.262	0.028
RANGE	30-75	32-74		

Of 50 subjects with 100 eyes in non- diabetic group 32 patients (32%) had symptoms of dry eye, while in diabetic group (50 subjects with 100 eyes) 68 patients (68%) complained of dry eye. A total of 100 subjects with 200 eyes, 90 eyes had symptoms of dry eye i.e. 45%. Prevalence of dry eye syndrome was significantly higher in poorly controlled diabetes along with more severe diabetic retinopathy.

Schirmer’s test was normal in 78 eyes in non diabetic group and 32 eyes of diabetic group. Largest number of eyes (n=40) in diabetic group has mildly abnormal schirmer’s test. Eight eyes in diabetic group while none in nondiabetic group had severe abnormality of schirmer’s test. Schirmer’s test was statistically abnormal in diabetic group (p 0.001) (table 2).

Table 2: Comparison of Schirmer’s test in diabetic and nondiabetic group

SCHIRMERS TEST	NON DIABETIC	DIABETIC	P VALUE
NORMAL	78	32	0.001
MILD	12	40	
MODERATE	10	20	
SEVERE	0	8	

Tear break up time was normal in 80 eyes in non -diabetic group and 30 eyes of diabetic group. Largest number of eyes (n=40) in diabetic group has mildly abnormal tear break up time. Ten eyes in diabetic group while none in non- diabetic group had severe abnormality of tear break up time. Tear break up time was statistically abnormal in diabetic group (p 0.001) (table 3).

Table 3 Comparison of tear break up time in diabetic and non diabetic groups

BUT	NON DIABETIC	DIABETIC	P VALUE
NORMAL	80	30	0.001
MILD	16	40	
MODERATE	4	20	
SEVERE	0	10	

In diabetic group 10 patients had mild, 8 had moderate, 5 had severe non proliferative diabetic retinopathy (NPDR), and 3 patients had proliferative diabetic retinopathy (PDR). Seventy four patients did not have evidence of retinopathy.

Higher grades of schirmer’s test abnormality were present with more severe form of diabetic retinopathy. A statistically significant relationship between severity by Schirmer’s test and severity of diabetic retinopathy was present (p value 0.0013). table 4.

Table 4: schirmer’s test abnormality in diabetic group with various grades of retinopathy

Schirmer Test	No Retinopathy eyes(74)	Mild NPDR Eyes(10)	Moderate NPDR(8)	Severe NPDR(5)	PDR(3)	P VALUE
Normal	28	2	0	0	0	0.0013
Mild	32	4	2	0	0	
Moderate	12	2	5	2	2	
Severe	2	2	1	3	1	

More severe grades of tear break up time abnormality was present with higher grades of retinopathy. A statistically significant relationship between severity of tear break up time and severity of diabetic retinopathy was present in patient with diabetes (p value 0.002) table 5

Table 5: Tear break up time abnormality in diabetic group with various grades of retinopathy

TBUT Test	No Retinopathy eyes(74)	Mild NPDR Eyes(10)	Moderate NPDR(8)	Severe NPDR(5)	PDR(3)	P V ALUE*
Normal	34	3	0	0	0	0.002
Mild	32	5	5	1	1	
Moderate	8	2	2	3	2	
Severe	0	0	1	1	0	

*Fisher' exact test

Discussion

In our study schirmer test and TBUT were significantly reduced in diabetic patients compared to non diabetics. These results suggest that dry eye is significant part of diabetic ocular surface disorder.

In our study 68 % patients in diabetic group while 32% patients in non diabetic group complained of

dry eye. Prevalence of dry eye syndrome was significantly higher in poorly controlled diabetes along with more severe diabetic retinopathy. Similar result was seen in study by Dr. R S Uma Devi et al wherein the prevalence of dry eyes was found to be 69% in diabetic. (15%, In Type 1 diabetes and 82%. In Type II,) ¹¹ Seifart and Stempel, found 57% of dry eye in Type I and 70% in Type II ¹².

Dry eye is a disorder of tear film due to tear deficiency or excessive tear evaporation. So both intrinsic and extrinsic factors play role in causation of symptoms. Evaporative dry eye may be affected by environmental condition such as high altitude, dryness/ extreme heat condition etc. India being the tropical country where extreme variation in weather condition may contribute dry eye symptoms (DES). Patients in our study were resident of hilly area; hence high altitude may also have contributed to DES.

DES was recognized as a lacrimal function unit (LFU) dysfunction disease by the International Dry Eye Workshop in 2007. The LFU which protects and maintains the tear film and normal function of the ocular surface is composed of “the cornea, conjunctiva, lacrimal gland, meibomian gland, lids, and the sensory and motor nerves that connect them”.¹³

DES is common among patients with DM, with tear film stability and TBUT being decreased. Tear film is composed of mucin aqueous and lipid component. The mucin layer of the tear film is necessary for tear film spreading and wetting. Deficiency in the mucous layer may reduce tear film stability and TBUT¹⁴. Tear hyperosmolarity and tear film instability caused by LFU and ocular surface dysfunction are the key factors in DES. Effects of hyperglycemia on any component of the LFU may be transferred to the entire system via neural connections, leading to insufficient tear production or excess tear loss, abnormalities in blinking, and changes in tear film composition¹⁵ Tear secretions are reduced in patients with DM as shown by the significantly decreased Schirmer’s test values as well as TBUT. The reduced Schirmer’s value is linked to an advanced stage of diabetic retinopathy. The reduction in reflex tearing may be due to a decrease in corneal sensitivity. Severe DM DES leads to visual impairment, corneal scarring, and ulcers, leading to secondary bacterial infections. The synergistic effect of corneal infection and diabetes accelerates corneal lesions, which irreversibly change the ocular surface and induce visual impairment¹⁶. Tear film dysfunction not only leads to the occurrence of dry eye but simultaneously aggravates the ocular surface,

which induces a corneal epithelial defect, a common sign in diabetics¹⁷. Aldose reductase is an important enzyme in the pathway involved in the pathogenesis of dry eye and oral administration of aldose reductase inhibitors has been demonstrated to improve tear dynamics¹⁸.

Insulin is critical for proliferation of the acinar lacrimal gland (LG) and cornea epithelial cells. Insulin partially reversed the decreased protein expression induced by LG dysfunction; this process is involved in supporting exocytosis and vesicular formation through insulin replacement therapy¹⁹. It has been demonstrated that hyperglycemia induces histological alterations in the lacrimal gland, suggesting the role of diabetes-induced oxidative stress in DES²⁰.

In our study diabetic patient had significantly lower values of schirmer and TBUT compared to nondiabetic group. Similar to our study Silviana S. Kamela et al on Egyptian population found that Schirmer’s and TBUT values were lower among the uncontrolled diabetes patients. It was statistically significant with bad metabolic control and duration of diabetes. Ozdemiret al.²¹ in his study did find that TBUT and Schirmer’s test values were significantly lower in diabetic subjects. In Goebels study Schirmer test and tearing reflex was significantly lower in diabetic patients compared with control group²².

In our study a statistically significant relationship between severity of tear break up time and severity of diabetic retinopathy was present in patient with diabetes (p value 0.002)

Significant associations have been identified between diabetic retinopathy (DR) and DES. In a hospital-based study by Nepp J et al, 17.1% of DES in patients with DM was found to have mild nonproliferative diabetic retinopathy (NPDR), 17.1% had moderate NPDR, 11.1% had severe nonproliferative diabetic retinopathy (NPDR), and 25.1% had proliferative diabetic retinopathy (PDR)²³.

In our study frequency of dry eye syndrome was higher in diabetic patients with DR, but we did not find any study like that and larger studies need to evaluate relation between dry eye and DR.

Prevalence of dry eye in our study is very high. It might be due to dry weather in this region and high prevalence of neurological disorder in type 2 diabetic patients.

Conclusion:

Diabetic patients are more prone to have dry eye disease than normal subjects. Diabetic patients must be evaluated for dry eye especially with diabetic retinopathy as this study and much other study shows positive correlation between severity of diabetic retinopathy with dry eye disease. Adequate glycemic control is also a very important criteria to avoid serious corneal complications. These abnormalities can result in severe complications of ocular surface.

Early examination of the diabetic patients for the detection of the dry eye is indicated so that we can manage dry eye in early stage and prevent dreadful corneal complications.

REFERENCES:

1. Idf diabetes atlas - 8th edition.
2. Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J PhysiolPathophysiol*. 2013;4(4):46-57
3. SainiJS, Khandalvla B. Corneal epithelial fragility in diabetes mellitus. *Cann J Ophthalmol* 1995;30:142-6.
4. Chaus P. Dry Eye and Diabetes Often Go Hand in Hand:dLife Blog. Connecticut:Life Med Media, Inc;2013. Available from: http://www.dlife.com/diabetes/complications/eye-care/chaus_sept2006.
5. Manaviat M. R., Rashidi M., Afkhami-Ardekani M., Shoja M. R. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC Ophthalmology*. 2008;8, article 10 doi: 10.1186/1471-2415-8-10
6. Tavakoli M, Kallinikos PA, Efron N, Boulton AJ, Malik RACorneal sensitivity is reduced and relates to the severity of neuropathy in patients with diabetes. *Diabetes Care*2007; 30:1895–1897
7. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). *Ocul Surf*2007;5:75–92
8. Schein OD, MUÑO B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *Am J Ophthalmol*. 1997;124:723–728.
9. Moss SE, Klein R, Klein BEK. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol*. 2000;118:1264–1268
10. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. *Eye*. 2009;23:688–693.
11. Dry Eye in Diabetes Mellitus Patients and its Relationship with Diabetic Retinopathy Dr. R S Uma Devi MS1, Dr. M S SmithaGowda MS2.
12. Seifart U, Stempel I. The dry eye syndrome and diabetes mellitus. *Ophthalmologe*. 1994; 91:235–239
13. Rieger G. The importance of the precorneal tear film for the quality of optical imaging. *British Journal of Ophthalmology*. 1992;76(3):157–158. doi: 10.1136/bjo.76.3.157.
14. Zhang X, Zhao L, Deng S, Sun X, Wang N. Dry eye syndrome in patients with diabetes mellitus: prevalence, etiology, and clinical characteristics. *Journal of ophthalmology*. 2016;2016.
15. Research in dry eye: report of the Research Subcommittee of the International Dry Eye Workshop (2007) *The Ocular Surface*. 2007; 5(2):179–193.
16. Lubniewski A. J., Houchin K. W., Holland E. J., et al. Posterior infectious crystalline keratopathy with *Staphylococcus epidermidis* *Ophthalmology*. 1990;97(11):1454–1459.
17. Inoue K., Kato S., Ohara C., Numaga J., Amano S., Oshika T. Ocular and systemic factors relevant to diabetic keratoepitheliopathy. *Cornea*. 2001;20(8):798–801.
18. Ramos-Remus C., Suarez-Almazor M., Russell A. S. Low tear production in patients with diabetes mellitus is not due to Sjogren's syndrome. *Clinical and Experimental Rheumatology*. 1994;12(4):375–380.
19. Dias A. C., Batista T. M., Roma L. P., et al. Insulin replacement restores the vesicular

- secretory apparatus in the diabetic rat lacrimal gland. *Arquivos Brasileiros de Oftalmologia*. 2015;78(3):158–163
20. Módulo C. M., Jorge A. G., Dias A. C., et al. Influence of insulin treatment on the lacrimal gland and ocular surface of diabetic rats. *Endocrine*. 2009;36(1):161–168.
 21. Ozdemir M, Buyukbese MA, Cetinkaya A, Ozdemir G. Risk factors for ocular surface disorders in patients with diabetes mellitus. *Diabetes Res ClinPract* 2003; 59:195–199.
 22. Goebbels M. Tear secretion and tear film function in insulin dependent diabetics. *Br J Ophtalmol*. 2000;84:19–21.
 23. Nepp J., Abela C., Polzer I., Derbolav A., Wedrich A. Is there a correlation between the severity of diabetic retinopathy and keratoconjunctivitis sicca? *Cornea*. 2000;19(4):487–491.