

Comparative Evaluation of Incidence of Dry Eye in Patients with and Without Diabetes Mellitus

Rajender S Chauhan^{1*}, Ashok Rathi¹, J. P Chugh², Neha Gandhi³, Apoorva Goel³

¹Professor, Regional Institute of Ophthalmology, Pt. B. D. Sharma, Postgraduate Institute of Medical Sciences, Rohtak-124001, India

²Sr Professor, Regional Institute of Ophthalmology, Pt. B. D. Sharma, Postgraduate Institute of Medical Sciences, Rohtak-124001, India

³Resident, Regional Institute of Ophthalmology, Pt. B. D. Sharma, Postgraduate Institute of Medical Sciences, Rohtak-124001, India

*Corresponding author: Dr. Rajender Sigh Chauhan | Received: 16.04.2019 | Accepted: 24.04.2019 | Published: 30.04.2019
DOI: [10.21276/sjmeps.2019.5.4.13](https://doi.org/10.21276/sjmeps.2019.5.4.13)

Abstract

Dry eye is defined as the disorder of the tear film either due to tear deficiency or excessive evaporation which causes damage to the inter-palpebral ocular surface which comprises of the entire epithelial surface of the cornea, limbus and conjunctiva. Dry eye disease (DED) affects 4.3-16% of adults approximately. There are various etiological factors associated with dry eye disease and diabetes mellitus is one of them. A case control study of 100 diabetic and 100 non diabetic patients was conducted at a tertiary care eye hospital to see the correlation with duration of diabetes. The mean duration of diabetes was 8.48±4.29 years. The mean fasting and post prandial blood sugar level in study group were 155.77±14.94 mg% and 263.77±51.49 mg% respectively. The difference of blood sugar level from control was statistically significant ($p < 0.001$). The TBUT, marginal tear strip staining, fluorescein staining, rose Bengal staining were found statistically significant in study group. 35 cases had moderate dry eye in diabetic group. The comparison of both the group was statistically significant. The severity of dry eye was statistically significant in > 10 years duration of diabetes. A total of 11% patients with >10 years duration were having severe dry eye as compared to only 2% of <10 years of diabetes. The difference between the incidence of dry eye in right and left eye was insignificant.

Keywords: Dry eye, Diabetes mellitus, Rose Bengal stain, TBUT, Lissamine green stain.

Copyright @ 2019: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Dry eye is defined as the disorder of the tear film either due to tear deficiency or excessive evaporation which causes damage to the inter-palpebral ocular surface which comprises of the entire epithelial surface of the cornea, limbus and conjunctiva. Tear film is a complex fluid secreted by orbital glands and ocular surface epithelial cells. There are three layers of tear film namely- lipid layer which is the most superficial layer and helps to retard evaporation, maintain optical properties of tear film and prevent damage to lid margin skin, aqueous layer which is the middle layer and works to supply oxygen to avascular cornea and maintains corneal and conjunctival epithelial cell function and the mucous layer which is the innermost layer and converts hydrophobic surface of cornea into hydrophilic surface [1].

Dry eye disease (DED) affects 4.3-16% of adults approximately. There are various etiological factors associated with dry eye disease and diabetes mellitus is one of them. Pathogenesis of dry eye disease is related to the dysfunction of lacrimal functional unit

(LFU) which is formed by lacrimal glands, ocular surface, sensory and motor nerves and lids [2]. Symptoms of DED include ocular irritation, burning, itching, foreign body sensation, photophobia, blurring of vision associated with redness of eyelids and conjunctiva. Signs include stringy mucous, particulate matter in the tear film, lusterless ocular surface, conjunctival xerosis, bitot's spots and filamentary keratitis [3].

Various modalities to diagnose DED are tear film break up time (TBUT), rose Bengal staining, schirmer's 1 test, lissamine green staining, tear pH test, marginal tear strip test, tear film osmolarity test, tear lactoferrin test, tear lysozyme test, ocular ferning test and conjunctival impression cytology [4-9].

Diabetes mellitus and its clinical association with dry eye is becoming a frequent and complicated problem in ophthalmology and many clinical studies have revealed that the clinical manifestations of diabetes mellitus are associated with lacrimal gland and ocular surface dysfunction possibly due to exocrine dysfunction of main lacrimal gland, diminished

sensitivity to stimulatory signals for lacrimal gland production due to diabetic neuropathy or abnormality in normal tear protein pattern like lactoferrin, lysozyme, lipocalin and albumin. Both total and reflex tear secretion are reduced [10]. The most frequent and measurable clinical findings are reduced tear secretion, tear film instability, higher grade of conjunctival squamous metaplasia, lower goblet cell density and reduced corneal sensation. Diabetes mellitus also reduce the lipid layer of tear film. Other features of DED in diabetes are Corneal and conjunctival epithelial alterations, persistent epithelial defects, corneal epitheliopathy, hyperosmolarity punctate keratopathy, recurrent erosions, persistent epithelial defects, neurotrophic keratopathy, delayed wound healing and higher risk of microbial keratitis [3].

As prevalence of diabetes mellitus and its ocular complications are increasing progressively in our country, this study has been conducted to analyze the incidence of dry eyes in diabetics.

MATERIAL AND METHODS

Study Design

- This case-control study was conducted in Regional Institute of Ophthalmology (RIO), Pt. B.D. Sharma PGIMS, Rohtak over a span of 1 year.
- The study group consisted of 100 diabetic patients and 100 non-diabetic individuals which served as the control group.
- The study investigated the incidence of dry eye in either group and evaluated the correlation of duration of diabetes with incidence of dry eyes.

Inclusion Criteria

100 individuals of either sex, between the age of 40-70 years, diagnosed to have diabetes mellitus of any duration were included in the study group. Control group included age and sex matched non-diabetic individuals.

Exclusion Criteria

- History of any other systemic or local disease known to cause dry eye other than diabetes mellitus.
- History of prolonged contact lens use
- History of ocular surgery in the past

After taking informed and written consent, detailed history including patient's particulars, nature of presenting complaints and associated conditions were recorded. Detailed history of diabetes including type, duration and nature of treatment along with fasting and postprandial blood sugar and HbA1C levels were also recorded.

A questionnaire of ocular symptoms pertaining to dry eye was prepared and presences of one or more symptoms often or all the time were taken as positive.

Examination

A brief general and systemic examination was carried out. Complete ocular examination was performed including best corrected visual acuity using Snellen's acuity chart, condition of lids, meibomian glands, conjunctival and corneal surface, anterior and posterior segment examination by slit lamp examination, intraocular pressure measurement and fundus examination.

Tear film evaluation was done in the following order

- **Precorneal tear film:** It was observed for the presence of debris.
- **Tear film break up time test (TBUT):** No anesthesia was used. A dry fluorescein strip was touched to the inferior fornix with the patient looking up. The cornea was scanned on the slit lamp under low magnification using the cobalt blue filtered light. The patient was instructed to blink once or twice and then stare straight ahead without blinking. The time period for appearance of the first dry spot since the last blink was calculated as TBUT. Value <10 seconds was taken as abnormal.
- **Marginal strip staining test:** Patient was allowed normal blinking and after 2-3 minutes, marginal strip stained with fluorescein was observed under diffuse cobalt blue light of slit lamp and graded as intact, scanty, markedly diminished or absent. Fluorescein staining of the cornea was noted for pattern such as fine punctate, coarse punctate or diffuse.
- **Schirmer's 1 test:** It was performed by placing a pre-cut strip of filter paper (Whatman filter paper No. 41) of size 35×5 mm at the junction of medial 2/3 and lateral 1/3 of the inferior cul-de-sac. Patient was instructed to blink normally and the amount of wetting of the paper strip after 5 minutes was measured. Wetting of ≤10 mm was taken as abnormal.
- **Rose Bengal and lissamine green staining:** A moistened strip of rose Bengal dye without anesthesia was applied in the inferior cul-de-sac. Van Bijsterveld scoring system was used to grade the staining of cornea and conjunctiva on a scale of 0-3 in 3 areas- nasal conjunctiva, temporal conjunctiva and cornea. Score of 0 was for absent staining, 1 for just present, 2 for moderate and 3 for gross staining. With this system, the maximum possible score was 9 and a score of more than 3 was considered positive for dry eye. Lissamine green staining was performed in a similar manner 30 minutes after rose Bengal staining. Dry eye was defined as one or more symptoms of dry eye

along with one or more positive clinical findings based on slit lamp examination and one or more positive clinical tests from the ones mentioned above.

The severity of dry eye was graded as per khurana's scoring system as described below-

S. NO.	Tear function test	Score			
		0	1	2	3
1	Tear film breakup time (in sec)	>10	6.1- 10	3.1- 6	0-3
2	Marginal tear strip staining	Intact	Scanty	Markedly diminished or discontinuous	Absent
3	Fluorescein staining	Absent	Fine punctate	Coarse punctate	Diffuse
4	Schirmer's 1 test 9in mm/5 min.)	>10	5-10	3-4	0-2
5	Rose Bengal staining	0-3	4-5	6-7	8-9
6	Lissamine green staining	0-3	4-5	6-7	8-9

Grading criteria	Total score	Severity of dry eyes
	0-1	No dry eye
	2	Dry eye suspect
	3-8	Mild dry eye
	9-13	Moderate dry eye
	14-18	Severe dry eye

Statistical Analysis

At the end of the study, the data was analyzed by using Chi- square method or student t- test.

Rohtak. It was a case control study in which 100 diabetic patients served as the study group and 100 non-diabetic individuals served as the control group. This study investigated the incidence of dry eyes in either group and evaluated the correlation of duration of diabetes with incidence of dry eyes.

OBSERVATIONS

The present study was conducted in Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS,

Table-1: Duration of diabetes in study population

Duration	No. of patients	Percentage (%)
Upto 5 years	27	27
6-10 years	39	39
11-20 years	34	34
>20 years	0	0
Mean ± SD	8.48 ± 4.29	

Table-2: Mean blood sugar in both the groups

Blood sugar (mg/dl)	Study group Mean ± SD	Control group Mean ± SD	Statistical significance
Fasting	155.77 ± 14.94	80.16 ± 8.85	<0.001 HS
Postprandial	263.77 ± 51.49	113.46 ± 12.27	<0.001 HS
HbA1c (%)	7.91 ± 1.42	-	

The difference in the blood sugar levels- both fasting and postprandial between the two groups was found to be statistically significant (p<0.001).

Table-3: Shows TBUT in study group and control group

Seconds	Score	Study group				Control group			
		No. of patients		%		No. of patients		%	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
>10	0	18	22	18	22	51	50	51	50
6.1- 10	1	27	29	27	29	19	21	19	21
3.1- 6	2	38	32	38	32	14	18	14	18
0-3	3	17	17	17	17	16	11	16	11
Statistical significance		$\chi^2 = 28.28; p < 0.001$ HS (right eye) $\chi^2 = 17.37; p < 0.001$ HS (left eye)							

We observed maximum number of patients with TBUT within 3.1- 6 seconds in study group i.e.

32% while in the control group, maximum number of patients (50%) had TBUT of more than 10 seconds and

statistical comparison showed high significance in both the groups.

Table-4: Marginal tear strip staining in study and control group

Staining	Score	Study group				Control group			
		No. of patients		%		No. of patients		%	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Intact	0	22	24	22	24	22	63	22	63
Scanty	1	35	40	35	40	35	21	35	21
Markedly diminished	2	22	20	22	20	22	8	22	8
Absent	3	21	16	21	16	21	8	21	8
Statistical significance		$\chi^2 = 29.13; p < 0.001$ HS (right eye) $\chi^2 = 31.21; p < 0.001$ HS (left eye)							

Table-4 Show marginal tear strip staining of the patients in the study and control group. We noted maximum number of patients (35%) had scanty staining in the study group, while maximum number of patients (58%) in the control group had intact staining and statistical comparison was found to be significant in the

right eye. We also noted that maximum number of patients (40%) had scanty staining in the study group, while maximum number of patients (63%) in the control group had intact staining and statistical comparison was found to be significant in the left eye.

Table-5: Fluorescein staining in study group and control group

Staining	Score	Study group				Control group			
		No. of patients		%		No. of patients		%	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Absent	0	14	20	14	20	32	32	32	32
Fine punctate	1	44	40	44	40	47	46	47	46
Coarse punctate	2	27	28	27	28	12	12	12	12
Diffuse	3	15	12	15	12	9	10	9	10
Statistical significance		$\chi^2 = 14.41; p < 0.01$ HS (right eye) $\chi^2 = 9.76; p < 0.05$ HS (left eye)							

Table-5 Depicts fluorescein staining in both eyes of the patients in study group and control group. In right eye, we noted maximum number of patients with fine punctuate staining i.e. 44% in study group and 47% in control group while a total of 14% cases of absent staining in study group and 32% cases in control group were found with significant statistical comparison in

both the groups. In left eye, we noted maximum number of patients with fine punctuate staining i.e. 40% in study group and 46% in control group while a total of 20% cases of absent staining in study group and 32% cases in control group were found with significant statistical comparison in both the groups.

Table-6: Schirmer's test in study and control group

Value	Score	Study group				Control group			
		No. of patients		%		No. of patients		%	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
>10	0	33	33	33	33	44	42	44	42
5- 10	1	25	35	25	35	43	34	43	34
3-4	2	30	21	30	21	11	15	11	15
0-2	3	12	11	12	11	2	9	2	9
Statistical significance		$\chi^2 = 22.28; p < 0.001$ HS (right eye) $\chi^2 = 2.29; p 0.513$ NS (left eye)							

Table-6 Shows schirmer's 1 test in study and control group in both the eyes. It was observed in right eye that maximum number of patients (33%) had schirmer's 1 test value of more than 10 mm at 5 minutes and in the control group 44% patients were having value of >10 mm at 5 minutes with significant

statistical comparison in both the groups. It was observed in left eye that maximum number of patients (33%) had schirmer's 1 test value of more than 10 mm at 5 minutes and in the control group 42% patients were having value of >10 mm at 5 minutes with significant statistical comparison in both the groups.

Table-7: Rose Bengal staining in study group and control group

Score	Study group				Control group			
	No. of patients		%		No. of patients		%	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
0-3	49	46	49	46	61	63	61	63
4-5	12	12	12	12	22	18	22	18
6-7	33	33	33	33	8	13	8	13

8-9	6	9	6	9	9	6	9	6
Statistical significance	$\chi^2 = 20.09; p < 0.001$ HS (right eye) $\chi^2 = 13.14; p < 0.01$ S (left eye)							

Table-7 Shows rose bengal staining in study group and control group. In right eye it was observed that maximum patients (49%) were having a score of 0-3 in the study group while 61% patients in control group were having a score of 0-3 with high statistical

significance in both groups. In left eye it was observed that maximum patients (46%) were having a score of 0-3 in the study group while 63% patients in control group were having a score of 0-3 with high statistical significance in both groups.

Table-8: Lissamine green staining in study group and control group

Score	Study group				Control group			
	No. of patients		%		No. of patients		%	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
0-3	43	43	43	43	61	62	61	62
4-5	21	15	21	15	20	18	20	18
6-7	18	25	18	25	12	10	12	10
8-9	18	17	18	17	7	10	7	10
Statistical significance	$\chi^2 = 9.17; p < 0.05$ S (right eye) $\chi^2 = 11.95; p < 0.01$ S (left eye)							

Table-8 Shows lissamine green staining in both control and study group. In right eye it was seen that maximum number of patients i.e. 43% had a score of 0-3 in the study group and 61% had a score of 0-3 in control group with high statistical significance. In left

eye it was seen that maximum number of patients i.e. 43% had a score of 0-3 in the study group and 62% had a score of 0-3 in control group with high statistical significance.

Table-9: Grading of dry eye

	score	Study group				Control group			
		No. of patients		%		No. of patients		%	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
No dry eye	0-1	16	18	16	18	30	31	30	31
Dry eye suspect	2	7	8	7	8	21	20	21	20
Mild dry eye	3-8	29	28	29	28	26	27	26	27
Moderate dry eye	9-13	33	31	33	31	17	17	17	17
Severe dry eye	14-18	15	15	15	15	6	5	6	5
Statistical significance	$\chi^2 = 20.40; p < 0.001$ Highly Significant (right eye) $\chi^2 = 17.69; p < 0.001$ Highly Significant (left eye)								

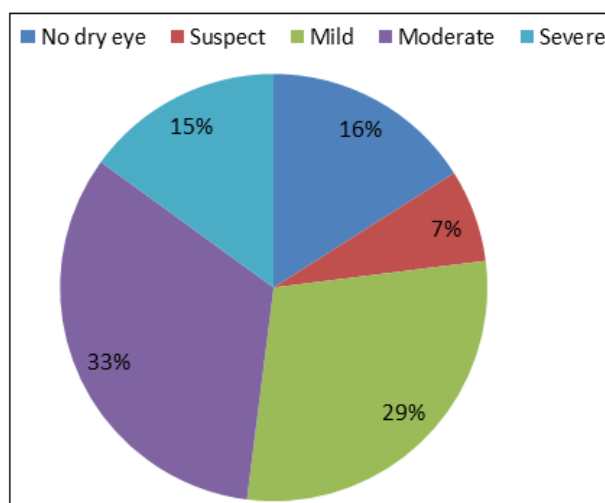


Chart-1: Showing distribution of patients according to duration of diabetes and severity of dry eyes in right eye of study group

Table-9 and Chart-1 Shows the analysis of dry eye in study and control group. in right eye, a total of 33% cases had moderate dry eye in study group and 17% patients in control group had moderate dry eye. In 18% cases of study group no dry eye was seen and in control group it was seen in 30% cases. In 15% of the cases in the study group severe dry eye was seen whereas in control group it was seen in only 6% cases. Statistical comparison of both groups was found to be

highly significant. In left eye, a total of 31% cases had moderate dry eye in study group and 17% patients in control group had moderate dry eye. In 18% cases of study group no dry eye was seen and in control group it was seen in 31% cases. In 15% of the cases in the study group severe dry eye was seen whereas in control group it was seen in only 5% cases. Statistical comparison of both groups was found to be highly significant.

Table-10: Relation of duration of diabetes with severity of dry eye

Duration in years	No dry eye		Dry eye suspect		Mild dry eye		Moderate dry eye		Severe dry eye	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
0- 5	7	6	3	3	7	8	8	8	2	2
6-10	8	11	4	4	13	11	12	11	2	2
11-20	1	1	0	1	9	9	13	12	11	11
Total	16	18	7	8	29	28	33	31	15	15
Statistical significance	$\chi^2 = 20.65; p < 0.01$ Significant (right eye) $\chi^2 = 19.23; p < 0.05$ Significant (left eye)									

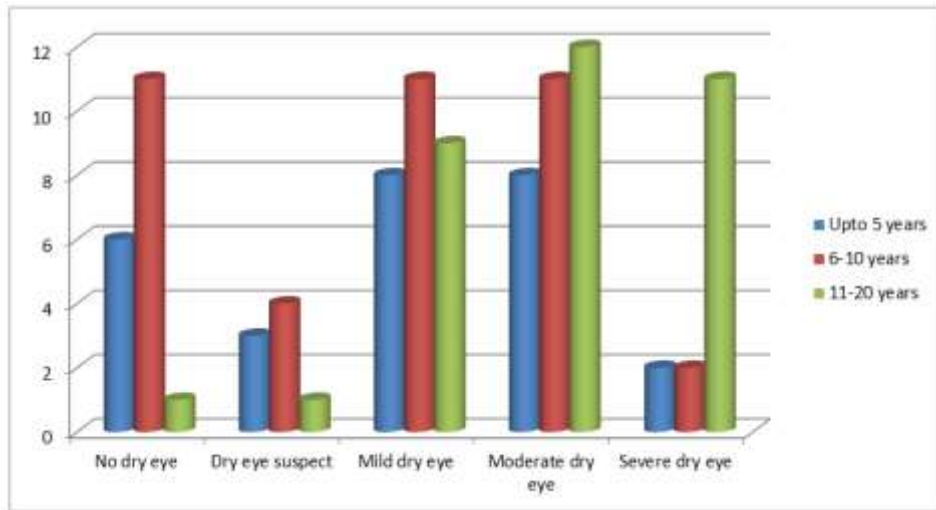


Chart-2: Duration of diabetes and severity of dry eyes

Table-10 and Chart-2 Shows that as the duration of diabetes increase, severity of dry eyes also increase. 11% of patients with duration of diabetes from 11-20 years were having severe dry eyes as compared to only 2% of patients with duration of diabetes from 6-10 years in left eye. On statistical analysis, the difference between the severity of dry eyes in diabetic patients with duration upto 10 years and with duration more than 10 years was found to be statistically significant. However, difference in the severity of dry eye in patients with duration of diabetes less than 5 years and with duration between 6-10 years was not statistically significant.

DISCUSSION

The present study was a case control study which was conducted in Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak. In this study 100 diabetic patients served as the study group and 100 non- diabetic individuals served as the

control group. This study was done to investigate the incidence of dry eyes in either group and evaluate the correlation of duration of diabetes with incidence of dry eyes.

There is no doubt that in the recent times, dry eye disease has become an extremely common condition that causes varying degree of ocular discomfort and disability. Reported prevalence of dry eye in the literature is diverse, varies both in western and Asian world, ranging between 7.8% in one study from western world and 93.2% in another study from asia [11, 12]. Prevalence of dry eye disease in western world was found to be 14.4% in Beaver Dam Eye Study done by Moss *et al.*, [13], 7.8% in women’s health study and 28.7% in another study done by Caffey *et al.*, in 1994 [11]. In Asian world, prevalence of dry eye has been reported as 33% by Schimura *et al.*, in 1999. Gupta *et al.*, [11, 12] has reported a prevalence of 54% in a study carried out in India. Epidemiological data shows that an increase in the number of patients with

this association is expected following the trend of rising number of diabetics worldwide and especially India, known as world capital of diabetes mellitus [14, 15].

The diagnosis of dry eyes was based on symptoms, signs, surface staining with fluorescein, lissamine green and rose Bengal stain and the diagnostic tests which included tear film break up time and schirmer's 1 test. In our study out of 100 diabetic patients, 39% of patients had diabetes for a duration ranging from 6-10 years followed by 345 patients with the duration of 11-20 years and remaining 27% of the patients were diabetics for less than 5 years. The prevalence of diabetic microvascular complications are higher in patients with longer duration of diabetes. Seifart and associates demonstrated that diabetic patients had an increased rate of keratoconjunctivitis sicca, which might be attributed to decreased corneal sensitivity, neuropathy involving innervation of lacrimal glands and loss of goblet cells [16].

In the present study, mean blood sugar levels were estimated in both the groups. Fasting mean blood sugar was 155.77 ± 14.94 mg/dl in study group as compared to 80.16 ± 8.85 mg/dl in control group. Similarly post prandial blood sugar was also very high in study group patients i.e. 263.77 ± 51.49 mg/dl as compared to 113.46 ± 12.27 mg/dl in the control group. Mean HbA1c in study group patients was 7.91 ± 1.42 . The difference in blood sugar levels both fasting and postprandial between the two groups was found to be statistically significant. Kaiserman and associates have reported that good blood sugar regulation was important for prevention and control of dry eye among diabetic patients [17].

In our study more than 70% diabetic patients were having TBUT <10 seconds and the difference between the TBUT of two groups was statistically significant. Similar findings have been observed in a study by Hasan *et al.*, who concluded that 67% of diabetic patients had TBUT <10 seconds [18]. In another study done by Seifart *et al.*, TBUT less than 10 seconds in 94.2% diabetic patients was seen as compared to TBUT of <10 seconds in only 9.4% of the non diabetic ones [19]. In a study by Khurana *et al.*, in 100 consecutive patients with dry eye along with 100 age and sex matched controls, marginal tear strip staining abnormality was observed in 93% of the patients with dry eye and in only 11% of control patients [20]. In a study done by Beckman et al on 38 diabetic and 25 non- diabetic patients, the mean conjunctival staining scores were significantly higher in the diabetic patient group [21]. Goebbel had reported that the schirmer's 1 test value was significantly reduced among diabetics [22]. Hasan *et al.*, reported that schirmer's 1 test value was <10 mm in 16% of diabetic patients. Schirmer's 1 test was positive in 60.86% of diabetic patients as studied by Rehman A *et al.*, [23].

Seifart and associates in 1994 demonstrated that diabetic patients had a prevalence of 70% dry eye disease [19]. In a cohort study on 3722 patients in 2000, Moss et al showed 18.1% of diabetics were having dry eye [13]. Nepp *et al.*, in 2000 showed 43% of diabetics were having dry eye in his study [24]. Hom and De land in 2000 showed that 52.9% of patients with either diabetes or borderline diabetes had self reported clinically relevant dry eye disease in them [17]. Beaver Dam Eye Study showed that 19.8% of type 2 diabetics had dry eyes [13]. Manaviat *et al.*, performed a study to assess the prevalence of dry eye disease in diabetes mellitus and noted 54.3% of the diabetics suffered from dry eye disease [25]. In a study by Najafi *et al.*, [26] the prevalence of dry eye disease was 27.7% and in another study by Tanushree et al the prevalence of dry eye disease in diabetics was found to be 36% [27].

CONCLUSION

Mild to moderate dry eye is comparatively more prevalent in diabetic patients, as the duration of diabetes increases, severity of dry eye also increases. A total of 11% patients with duration of diabetes from 11-20 years were having severe dry eye as compared to only 2% of patients with duration of diabetes from 6-10 years in both eyes. The difference between the incidence of dry eye in right eye and left eye in diabetic patients was found to be insignificant ($p > 0.05$).

REFERENCES

1. Bron, A. J., Tiffany, J. M., Gouveia, S. M., Yokoi, N., & Voon, L. W. (2004). Functional aspects of the tear film lipid layer. *Experimental eye research*, 78(3), 347-360.
2. Stern, M. E., Beuerman, R. W., Fox, R. I., Gao, J., Mircheff, A. K., & Pflugfelder, S. C. (1998). The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea*, 17(6), 584-589.
3. American Academy of Ophthalmology Basic and Clinical Science Course subcommittee. (2008). Basic and Clinical Science Course. External Disease and Cornea: Section 8, San Francisco, CA. American Academy of Ophthalmology, 71-72.
4. Pflugfelder, S.C., Tseng, S.C., Sanabria, O. (1998). Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea*, 17(1), 38-56.
5. Feenstra, R. P., & Tseng, S. C. (1992). Comparison of fluorescein and rose bengal staining. *Ophthalmology*, 99(4), 605-617.
6. Norn, M. S. (1973). Lissamine green: Vital staining of cornea and conjunctiva. *Acta ophthalmologica*, 51(4), 483-491.
7. Manning, F. J., Wehrly, S. R., & Foulks, G. N. (1995). Patient tolerance and ocular surface

- staining characteristics of lissamine green versus rose bengal. *Ophthalmology*, 102(12), 1953-1957.
8. Farris, R. L., Gilbard, J. P., Stuchell, R. N., & Mandel, I. D. (1983). Diagnostic tests in keratoconjunctivitis sicca. *Eye & Contact Lens*, 9(1), 23-28.
 9. Clinch, T. E., Benedetto, D. A., Felberg, N. T., & Laibson, P. R. (1983). Schirmer's test: a closer look. *Archives of ophthalmology*, 101(9), 1383-1386.
 10. Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, 414(6865), 813-820.
 11. Schaumberg, D. A., Sullivan, D. A., Buring, J. E., & Dana, M. R. (2003). Prevalence of dry eye syndrome among US women. *American journal of ophthalmology*, 136(2), 318-326.
 12. Bukhari, A., Ajlan, R., & Alsaggaf, H. (2009). Prevalence of dry eye in the normal population in Jeddah, Saudi Arabia. *Orbit*, 28(6), 392-397.
 13. Moss, S. E., Klein, R., & Klein, B. E. (2000). Prevalence of and risk factors for dry eye syndrome. *Archives of ophthalmology*, 118(9), 1264-1268.
 14. Rieger, G. (1992). The importance of the precorneal tear film for the quality of optical imaging. *British journal of ophthalmology*, 76(3), 157-158.
 15. King, H., Aubert, R. E., & Herman, W. H. (1998). Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes care*, 21(9), 1414-1431.
 16. Toda, I., D Sullivan, B. E. N. J. A. M. I. N., Rocha, E. M., Da Silveira, L. A., Wickham, L. A., & Sullivan, D. A. (1999). Impact of gender on exocrine gland inflammation in mouse models of Sjögren's syndrome. *Experimental eye research*, 69(4), 355-366.
 17. Kaiserman, I., Kaiserman, N., Nakar, S., & Vinker, S. (2005). Dry eye in diabetic patients. *American journal of ophthalmology*, 139(3), 498-503.
 18. Hasan, I. N., Aggarwal, P., Gurav, A., & Patel, N. (2014). Assessment of dry eye status in type 2 diabetic patients in tertiary health care hospital, India. *IOSR J Dental Med Sci*, 13, 6-11.
 19. Seifart, U., & Stempel, I. (1994). The dry eye and diabetes mellitus. *Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft*, 91(2), 235-239.
 20. Khurana, A. K., Chaudhary, R., Ahluwalia, B. K., & Gupta, S. (1991). Tear film profile in dry eye. *Acta ophthalmologica*, 69(1), 79-86.
 21. Beckman, K. A. (2014). Characterization of dry eye disease in diabetic patients versus nondiabetic patients. *Cornea*, 33(8), 851-854.
 22. Göbbels, M., & Spitznas, M. (1992). Corneal epithelial permeability of dry eyes before and after treatment with artificial tears. *Ophthalmology*, 99(6), 873-878.
 23. Rahman, A., Yahya, K., Ahmed, T., & Sharif-ul-Hasan, K. (2007). Validity of symptoms as a screening tool for dry eye. *Pak J Ophthalmol*, 23(4), 198-203.
 24. Nepp, J., Abela, C., Polzer, I., Derbolav, A., & Wedrich, A. (2000). Is there a correlation between the severity of diabetic retinopathy and keratoconjunctivitis sicca?. *Cornea*, 19(4), 487-491.
 25. Manaviat, M. R., Rashidi, M., Afkhami-Ardekani, M., & Shoja, M. R. (2008). Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC ophthalmology*, 8(1), 10.
 26. Aghili, R., Khamseh, M.E., Fallah, A.E. et al. (2013). Dry eye and its correlation to diabetes microvascular complications in people with type 2 diabetes mellitus. *Journal of Diabetes and its Complications*, 27(5), 459-462.
 27. Tanushree, V., Madhusudhan, C. N., Hemalatha, K., Goiwda-Venkate, H. Y., & Acharya, A. A. (2014). Prevalence of dry eye in type 2 diabetes mellitus. *International Journal for Scientific Research and Development*, 2(1), 119-123.