



## Research Article

# Correlation of Severity of Dry Eye Disease in Diabetic Patients: A Clinical Study

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## Abstract

**Introduction:** *Diabetes Mellitus is one of the major health problems in developed and developing countries and it affects the organs due to micro-vasculopathy and neuropathy. Dryness of eye is also a finding frequently found and aggravated in diabetic patients. Although it appears to be a trivial complaint, but it can hamper day to day activities due to the discomfort caused by its symptoms.*

**Aim:** *The aim of this study was to estimate the presence of dry eye disease in patients having diabetes mellitus and to correlate dry eye disease with the stages of diabetic retinopathy.*

**Materials and Methods:** *200 Patients having type 2 diabetes mellitus were evaluated in this observational, cross sectional hospital based study using subjective and objective parameters like Ocular surface disease index questionnaire, tear film break up time, Schirmer's test, fluorescein staining, impression cytology, indirect ophthalmoscopy using ETDRS criteria.*

**Results:** *There was a significant correlation between dry eye disease, diabetic retinopathy and HbA1c*

**Conclusion:** *In conclusion, the results of the present study indicate that the diabetic subjects have an elevated frequency of dry eye disease (71.5% in this study). Hence examination for dry eye should be an integral part of the ocular assessment of patients with diabetes mellitus.*

## Introduction

Diabetes Mellitus (DM) has topped the leading health related catastrophes the world ever witnessed.<sup>[1]</sup> By 2040, the prevalence of diabetes globally would raise to 642 million.<sup>[2]</sup> Autonomic neuropathy that occurs as a part of diabetic polyneuropathy has been attributed to the insufficient production of tears in diabetes mellitus. The condition is affecting the nerves that

control the lacrimal gland secretion damaging the production of tear film that normally produce moisture to keep the eyes well lubricated.<sup>[3,4]</sup> When the transparent and sensitive cornea is no longer adequately lubricated, the cells of the cornea become damaged and free nerve endings are exposed. This exposure of the nerve endings lead to symptoms of dry eye.<sup>[5]</sup>

Insufficient tear production and changes in osmolarity promote high concentrations of proteins within the tears inducing apoptosis of surface epithelium and a vicious cycle of increased expression of inflammatory cytokines from ocular surface.<sup>[6]</sup> The condition gets even worse by apoptosis and decreased mucin production by goblet cells.<sup>[5,7]</sup> The prevalence of DES in diabetes has been reported to be up to 54.3%. DES leads to visual and ocular discomfort and can be complicated by epithelial defects, erosions or ulcers on the cornea and thereby compromising the quality of life. Therefore, as growing public health problem it must be diagnosed and treated.<sup>[8,9]</sup>

This research was undertaken to study the prevalence of dry eye in type 2 diabetic patients and to highlight the significance of careful examination for dry eye in these subgroup of patients so as to relieve the patients symptomatically and also to prevent the adverse complications of dry eye disease

### Methods

This study was an observational, cross sectional hospital based study on 200 patients and was conducted in the Department of Ophthalmology, Muzaffarnagar Medical College, Muzaffarnagar, from December 2017 to June 2019. This study was approved by Institutional Ethical Committee and informed consent was taken prior to the study.

### Inclusion Criteria

All patients with history of diabetes mellitus willing to participate in study, in the age group of 35-70 years, diagnosed to have diabetes mellitus type 2 referred from the department of Internal Medicine, Muazaffarnagar Medical College.

### Exclusion Criteria

- 1) Eyelid disease: Facial paralysis, ptosis, ectopion, entopion.
- 2) Conjunctival disease- Pterygium, conjunctivochalasis.
- 3) History of ocular surgery, chemical injury or use of topical medications.

- 4) Presence of systemic disorders- Sjogrens, Systemic lupus erythematosus, etc.

### Study Procedure

#### Method of Data Collection

##### 1) History

After taking written and informed consent, a detailed history regarding patient's symptoms was recorded.

##### 2) Questionnaire

#### OSDI (Ocular surface disease index).<sup>[10]</sup>

The OSDI questionnaire is used to objectivize the patient's symptoms.

It was adapted and explained to the patient and their responses were recorded.

##### 3) Examination

Each patient underwent through examination for the following parameters by a single examiner.

A) Cornea was evaluated on a slit lamp bio-microscope along with examination of corneal sensations.

B) Tear break up time measurement, the time of appearance of the first dry spot formation from the last blink measured the tear film BUT.

C) Schirmer's test with and without Anesthesia (basal and reflex tearing) It was performed by placing a Schirmer's strip in the inferior cul-de-sac, the amount of wetting of the strip after 5 minutes was measured.

D) Fluorescein staining of cornea was graded from 0-3 depending upon the amount of corneal epithelial surface involvement.

E) Impression cytology was performed using a millipore cellulose paper and dry eye severity was graded according to the Nelson's grading system.<sup>[11]</sup>

F) DEWS classification<sup>[12]</sup> was also adapted to grade dry eye disease.

G) Detailed fundus examination was performed and diabetic retinopathy if present was classified on the basis ETDRS classification.<sup>[13]</sup>

**Statistical Analysis:** The statistical analysis was performed by statistical software SPSS version 21.0. The Quantitative variables were present in

the form of mean and SD and the Qualitative variables were present in the form of frequency and percentage. The student t-test was used to compare the mean values between the 2 groups.

**Results**

There were 88 (44.0%) males and 112 (56.0%) females among the study population. The age range of the study population was 50.14±12.48 years. The mean HbA1c and disease duration was

compared between subjects with different severity of retinopathy using the One-way ANOVA test with post-hoc bonferroni test for inter-group comparisons. These parameters were significantly more among the subjects with severe NPDR and PDR than mild and moderate NPDR which inturn was significantly more than the normal subjects. Here p value being <0.5, implied that the relationship was statistically significant.

**Table 1:** Comparison of mean HBA1c between subjects with different severity of retinopathy

	HbA1c				
	Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
Normal (1)	5.94	0.47	44.533	<0.001*	4, 5 > 3 > 2 > 1
Mild NPDR (2)	6.36	0.24			
Moderate NPDR (3)	6.75	0.38			
Severe NPDR (4)	7.05	0.40			
PDR (5)	7.25	0.62			

**Table 2:** Comparison of mean disease duration between subjects with different severity of retinopathy

	Duration (in years)				
	Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
Normal (1)	0.00	0.00	197.074	< 0.001*	5 > 4 > 3 > 2 > 1
Mild NPDR (2)	6.29	2.66			
Moderate NPDR (3)	9.33	1.55			
Severe NPDR (4)	14.62	2.80			
PDR (5)	18.51	4.25			

**Table 3:** Comparison of mean Tear film breakup time between subjects with different severity of retinopathy

Tear film breakup time		Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
Right eye	Normal (1)	10.94	2.58	8.440	0.002*	4, 5 > 2, 3 > 1
	Mild NPDR (2)	9.12	3.34			
	Moderate NPDR (3)	8.15	2.85			
	Severe NPDR (4)	7.43	3.52			
	PDR (5)	7.30	4.18			
Left eye	Normal (1)	10.51	2.76	7.572	0.001*	4, 5 > 2, 3 > 1
	Mild NPDR (2)	9.00	3.74			
	Moderate NPDR (3)	8.20	2.95			
	Severe NPDR (4)	7.24	3.91			
	PDR (5)	7.09	4.12			

**Table 4:** Comparison of mean Schirmer’s values between subjects with different severity of retinopathy

Schirmers test		Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
Right eye	Normal (1)	15.22	4.53	9.112	0.001*	1 > 2 > 3 > 4, 5
	Mild NPDR (2)	12.00	5.61			
	Moderate NPDR (3)	11.01	4.60			
	Severe NPDR (4)	9.71	5.75			
	PDR (5)	9.50	6.72			
Left eye	Normal (1)	15.59	4.47	8.911	0.003*	1 > 2 > 3 > 4, 5
	Mild NPDR (2)	12.38	5.03			
	Moderate NPDR (3)	11.23	4.96			
	Severe NPDR (4)	9.33	6.18			
	PDR (5)	9.07	6.21			

**Table 5:** Correlation between dry eye (DEWS classification) and severity of diabetic retinopathy

DEWS CLASSIFICATION (Dry eye)	Severity of retinopathy				
	Normal	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Normal	59	0	0	0	0
	75.6%	0.0%	0.0%	0.0%	0.0%
Mild dry eye	14	39	1	0	0
	17.9%	92.9%	4.2%	0.0%	0.0%
Moderate episodic or chronic dry eye	0	3	21	0	0
	0.0%	7.1%	87.5%	0.0%	0.0%
Severe frequent or constant without stress dry eye	5	0	2	17	5
	6.4%	0.0%	8.3%	81.0%	14.3%
Severe and/or disabling and constant dry eye	0	0	0	4	30
	0.0%	0.0%	0.0%	19.0%	85.7%
Total	78	42	24	21	35
	100.0%	100.0%	100.0%	100.0%	100.0%

**Chi-square value = 508.719, p-value < 0.001\***

**Table 6:** Correlation between dry eye (OSDI scoring system) and severity of diabetic retinopathy

OSDI (Dry eye)	Severity of retinopathy				
	Normal	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Normal	60	0	0	0	0
	76.9%	0.0%	0.0%	0.0%	0.0%
Mild	10	39	0	0	0
	12.8%	92.9%	0.0%	0.0%	0.0%
Moderate	8	3	18	0	2
	10.3%	7.1%	75.0%	0.0%	5.7%
Severe	0	0	6	21	33
	0.0%	0.0%	25.0%	100.0%	94.3%
Total	78	42	24	21	35
	100.0%	100.0%	100.0%	100.0%	100.0%

**Chi-square value = 380.117, p-value < 0.001\***

**Table 7:** Correlation between dry eye (Nelson’s grading system and severity of diabetic retinopathy)

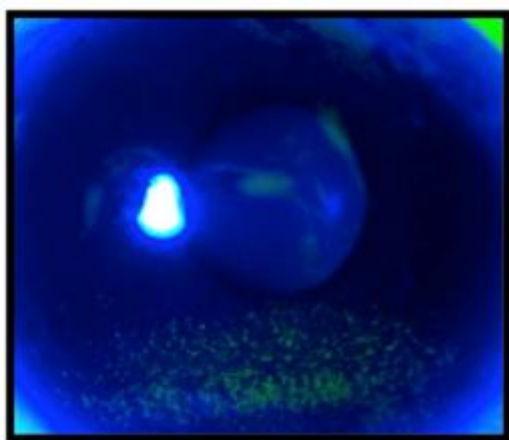
Dry eye as per Conjunctival impression cytology	Severity of retinopathy				
	Normal	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Grade 0	52	0	0	0	0
	66.7%	0.0%	0.0%	0.0%	0.0%
Grade 1	20	35	1	0	0
	25.6%	83.3%	4.2%	0.0%	0.0%
Grade 2	2	7	21	1	0
	2.6%	16.7%	87.5%	4.8%	0.0%
Grade 3	4	0	2	20	35
	5.1%	0.0%	8.3%	95.2%	100.0%
Total	78	42	24	21	35
	100.0%	100.0%	100.0%	100.0%	100.0%

**Chi-square value = 361.101, p-value < 0.001\***

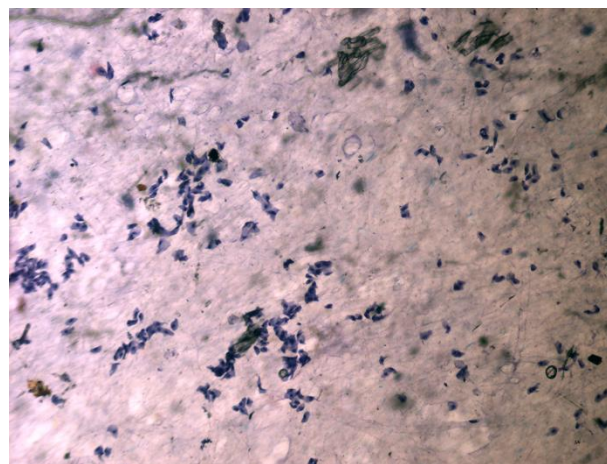
As per **DEWS classification**, Mild dry eye was present amongst 54 (27.0%), Moderate episodic or chronic dry eye was present among 24 (12.0%), Severe frequent or constant without stress dry eye was present amongst 29 (14.5%) and Severe and/or disabling and constant dry eye was present amongst 34 patients (17.0%).

As per **OSDI classification**, Mild dry eye was present among 49 (24.5%), Moderate dry eye was present among 31 (15.5%), Severe dry eye was present among 60 patients (30.0%).

As per **Conjunctival impression cytology**, Nelson’s Grade 1 dry eye was present amongst 56 (28.0%), grade 2 dry eye was present amongst 31 (15.5%), grade 3 dry eye was present amongst 61 patients.(30.5%).



**Fig: 1** Fluorescein staining grade 1 examined under cobalt blue filter.



**Fig: 2** Impression cytology image showing Nelsons grade 1 changes.

**Discussion**

The diabetic subjects in the current study had a high frequency of dry eye symptoms. In our study abnormal OSDI scores, TBUT, Schirmer’s test and ocular surface staining were noted in diabetic patients. Moreover, a positive association was noted between dry eye status and severity of diabetic retinopathy. The mean age in this study was 52.19 years with a standard deviation of 8.99. The majority of respondents were in the 56 to 65 year age group (mode 60 years). In current study, there were 44.0% males and 56.0% females among the study population. In present study, 42 (21.0%) had mild, 24 (12.0%) had moderate, 21 (10.5%) had severe NPDR and 35 (17.5%) had PDR.

According to the various studies in literature, the prevalence of dry eyes varies from 18.1% to 70%,

thereby showing wide disparity. There disparity is because there is no standardization of patients selected for studies, as the condition is multifactorial, subjective and objective tests and a lack of consensus on the criteria to diagnose dry eye. In our study, the average prevalence of dry eye disease by different methods within diabetics was 71.5%.

A significant correlation between dry eye disease and diabetic retinopathy was found in our study. Dry eye disease was more prevalent in people with severe NPDR and proliferative diabetic retinopathy and both dry eye and retinopathy had significant correlation with HbA1C ( $p < 0.001$ ).<sup>[14]</sup>

#### **TBUT and Schirmer's test**

Our study found results showing that the patients with diabetic retinopathy had a 6.65 times more chance of having Schirmer's value  $\leq 10$ mm than those without diabetic retinopathy. Also, patients with diabetic retinopathy had 6.37 times more chance of having TBUT  $\leq 10$  seconds than those without diabetic retinopathy. These finding can be attributed to derangement of corneal sensitivity and advancement in the stage of retinopathy.<sup>[15-18]</sup>

#### **OSDI**

In our study, as per OSDI classification, mild, moderate and severe dry eye was present among 49 (24.5%), 31 (15.5%) and 60 (30.0%) patients respectively. Diabetic polyneuropathy leads to an altered perception of symptoms and hence may not correlate the severity of the disease.<sup>[6,7]</sup>

#### **Conjunctival impression cytology**

In current study, as per Conjunctival impression cytology, Nelson's Grade 1 dry eye was present among 56 (28.0%), grade 2 dry eye among 31 (15.5%), grade 3 among 61 (30.5%) patients. Goblet cell density illustrates the condition of the ocular surface, its changes occur in response to alterations of the overlying tear film homeostasis. The loss of goblet cells is a sign of squamous metaplasia.

This study being a cross sectional observational type and with a small sample size, the interpretation of the subgroup outcomes should be

done with caution. The present study could therefore stimulate researchers to further undertake research with better study design and a larger sample size to further study these associations noted among diabetics.

#### **Conclusion**

According to this study, diabetics have a high frequency of dry eye disease. So, the clinical implication for physicians should be that the examination of dry eye must be stressed upon during the ocular evaluation of diabetic patient. It was also noted that the severity of dry eye was proportional to the severity of diabetic retinopathy. We therefore suggest that patients with diabetes should be screened for DES and probably treated long-term for the prevention of ocular surface damage in addition to screening for retinopathy. Our findings are consistent with the available literature on the same.<sup>[8,19-22]</sup>

Diabetic patients have a more severe ocular surface disease as the function and quality of the tears is poor along with subnormal ocular surface. Patients with diabetic retinopathy had poorer tear function tests and ocular surface parameters than those without changes of diabetic retinopathy. The high prevalence of severe dry eyes in diabetics, found in this study also suggests that the presence of dry eye disease in routine patients should raise a suspicion of the possibility of diabetes mellitus and such patients should be investigated for the same.

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