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Prevalence of dry disease in patients of type 2 diabetes mellitus: A cross-sectional study

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Abstract
Background and Aim: Dry eye disease has a significant impact including physical, social, psychological, negatively affecting daily activities and workplace productivity. This study is conducted to find the prevalence of dry disease in patients of type 2 diabetes mellitus and to find the correlation between glycemic control and prevalence of dry eye.
Material and Methods: A total of 130 patients fulfilled the criteria and total 200 eyes are included in the study. Type II diabetic patients diagnosed by the American Diabetes Associations criteria. The duration of diabetes, fasting and post-prandial blood sugar and Hb1Ac values were recorded. A complete ocular examination of the lid margins, conjunctiva, cornea and tear film was done. Examination of fundus was done to access the grade of diabetic retinopathy in the patients. Relevant examination of other important ocular structures was done. Following this, tests to diagnose dry eye were performed. These are tear break up time (TBUT), ocular surface staining by Rose Bengal and fluorescein staining, Schirmer's tests and conjunctival impression cytology. Diagnosis of dry eye was made if OSDI Score was more than 12 with one of the positive specific tests for dry eye.
Results: Prevalence of dry eye in diabetes in males and females were comparable to each other that are 44.99% and 54.01%. A statistically significant co-relation was found on comparing between Schirmer score of that eye and HbA1c level of that individual. All the patient with severe NPDR and PDR had Schirmer score of below 5 mm. Our study found that with increased duration of diabetes, the chance of developing dry eye increases, and poor glycemic control increases the severity of dry eye. The severity of diabetes has a positive correlation with goblet cell loss and morphological changes in conjunctival impression cytology.
Conclusion: Significant correlation between the prevalence of dry eye in the diabetic patient which shows poor glycemic control is directly related to dry eye. This study reveals that attention should also be paid on dry eye, particularly among patients suffering from DM when they are concerned about diabetic retinopathy.

Keywords: Conjunctiva, cytology, diabetes, dry eye

Introduction
Diabetic mellitus is a clinical syndrome characterized by hyperglycemia caused by absolute or relative deficiency of insulin [1]. The term diabetes was 1st coined by Arashes Cappodocia (81-133AD). Later, the word mellitus was added by Thomas Willis in 1675. Clinical features similar to diabetes mellitus (DM) were described 3000 years ago by the ancient Egyptians [2]. The refractive changes, cataract, nerve palsies, retinopathy, glaucoma, and macular edema were the common ocular morbidities arising from diabetes [3]. However, the ocular surface dryness, foreign body sensation, burning sensation, and grittiness of the eye also have been reported [4, 5]. It has been documented in literature that 18–70% of the patients with diabetes develop dry eye disease [6-10]. As per various studies, people with diabetes are more prone to suffer from dry eye disease than those without diabetes [11-14].
Dry eye disease (DED) is defined as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film accompanied by ocular symptoms, in which tear film hyperosmolarity, instability, ocular surface damage and inflammation, and neurosensory abnormalities play etiological roles [15]. Etiopathogenesis of dry eye in diabetes can be explained in terms of the factors related to peripheral neuropathy secondary to hyperglycemia, insulin insufficiency, inflammation, autonomic dysfunction, and altered enzyme aldose reductase activity [16, 17]. Some researchers also claimed that dry eye in diabetes can be caused by diabetes induced histological alteration in lacrimal gland and hyperglycemia-related oxidative stress [18].
Dry eye disease has a significant impact including physical, social, psychological, negatively affecting daily activities and workplace productivity.

DED has a substantial economic impact as a result of these QoL effects [19, 20].

This study is conducted to find the prevalence of dry disease in patients of type 2 diabetes mellitus and to find the correlation between glycemic control and prevalence of dry eye.

Material and Methods

The clinical observational study was conducted for a period of one year. A total of 130 patients fulfilled the criteria and total 200 eyes are included in the study. All the patients with type 2 diabetes mellitus fulfilling the inclusion and exclusion criteria over the study period was included in the study and received a detailed workup.

The patients were diagnosed to have type 2 diabetes of any duration and age 40 years or more was included in this study. Exclusion criteria: The patients with systemic disease and local ocular disease/surface abnormalities as assessed by history and clinical examination, other than DM, which are known to cause dry eye/ocular surface abnormalities, patients on anti-glaucoma topical medicine, 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, and patients who underwent any ocular surgery including LASIK surgery were excluded from this study.

Type II diabetic patients diagnosed by the American Diabetes Associations criteria [10, 11]. The duration of diabetes, fasting and post-prandial blood sugar and Hb1Ac values were recorded. An ocular surface disease (OSDI) questionnaire was administered to all participants to assess the symptoms of dry eye and correlate them with the signs. A complete ocular examination of the lid margins, conjunctiva, cornea and tear film was done. Examination of fundus was done to access the grade of diabetic retinopathy in the patients. Relevant examination of other important ocular structures was done. Following this, tests to diagnose dry eye were performed. These are tear break up time (TBUT), ocular surface staining by Rose Bengal and fluorescein staining, Schirmer's tests and conjunctival impression cytology.

Tear film break up time (TBUT) is the time in seconds between the last blink and the appearance of the dry spot. After instilling a drop of 2% fluorescein into the right eye, the patient was asked to blink a few times and place his head in the slit lamp. Then he/she was asked to look straight ahead without blinking. The tear film was observed, watching for an area of tear film rupture manifested by 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. Break up time of less than 10 seconds was considered positive, indicative of dry eye. Greater than or equal to 10 seconds was considered negative. Ocular surface staining is a measure of assessing ocular surface damage using sodium fluorescein or rose Bengal. Staining of the cornea is done by first placing a drop of sterile saline on a sterile fluorescein strip. The fluorescein strip is then placed in the inferior cul de sac of the eye by pulling down on the lower lid and then gently touching the bulbar conjunctiva with the fluorescein strip. The eye was examined for staining of cornea and conjunctiva using cobalt blue filter of slit lamp. Optimal viewing is between 1 and 3 min after instillation. A positive result is > 5 corneal spots. Similarly, rose Bengal strip is then placed in the inferior cul de sac and after 15 seconds, this eye was examined for staining of cornea and conjunctiva. Schirmer's test was performed before the other tests as it had to be done before instillation of anaesthesia. It was done using 5×35mm sterile strips of Whatman No.41 filter paper. Patient was made to sit in relatively dark room with fan switched off. The terminal round end of the strip was folded at the pre marked area. 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 2/3rd and lateral 1/3rd 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 patient was advised to blink normally. At the end of 5 minutes, the strips were removed and the length of filter paper moistened was measured in mm starting from the fold. More than 10mmof wetting after 5 min was considered normal, 8–10mm of wetting was considered mild dryness, 5–7mm of wetting was considered moderate dryness, and less than 5mm of wetting was considered severe dryness at the end of 5 min. Conjunctival impression cytology was conducted using cellulose acetate strips having a pore diameter of 0.45µm cellulose that were cut into wedge shaped pieces. The patient was lied in supine position, a drop of proparacaine hydrochloride 0.5% was instilled into the eye. After inserting a wire speculum, the wedge shaped filter paper strips was applied on the temporal bulbar conjunctiva with the help of a blunt smooth edged forceps. A smooth glass rod was used to press the paper gently. The strip was then removed with a peeling motion after 2-3 seconds. The strips were gently pressed over clean glass slide and the slides were fixed with 95% ethanol till further staining. Four such impressions were taken for each patient, two for each eye. The slides were stained using PAS stain and H and E stain. The epithelial cell morphology and Goblet cell counting was done to grade them according to standard criteria proposed by Nelson [12].

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

A total of 115 patients fulfilled the criteria and total 200 eyes are included in the study. The 30 eyes of that patient were excluded from the study due to history of ocular surgery. The age group of the patient included in the study was 33- 76 years mean age being 52.10 years. It was noted that with increasing age the chance of dry eye increases. The finding was statistically significant. The male and females were almost equal that is 61 and 54. Prevalence of dry eye in diabetes in males and females were comparable to each other that are 44.99% and 54.01%. The difference in prevalence between male and female is statistically not significant. The most common symptoms that the patient presented were increased frequency of blinking, itching, and eye fatigue. The Ocular Surface Disease Index (OSDI) questioner was given to every patient and score was recorded. On plotting the OSDI score to the HbA1c level it

was found that the diabetics with high HbA1c levels had increased OSDI score implying more severe symptoms.

In our study most participants were in the range 6.5-11 years and it was found that with increased duration of diabetes the chance of developing dry eye increases. Our study showed that the number of eyes with the Schirmer score more than 15 mm was 70, between 10-15 and 5-10 was 52 and 48 respectively, and below 5 mm there were 30 eyes. A statistically significant co-relation was found on comparing between Schirmer score of that eye and HbA1c level of that individual. In this study out of 200 eyes there were 44(22%) eyes had retinopathy. Twenty four eyes had mild NPDR, 16 had moderate NPDR, 5 had severe NPDR and 4 had PDR. In eyes with Schirmer score less than 5mm the mean FBS was 227.5 mg/dl, mean PPBS was 358.9 mg/dl and mean HbA1c was 10.5%, these values shows marked derangements in glycemic control in those patients.

This is in contrast to eyes whose Schirmer test score was more than 15 mm with mean FBS, PPBS and HbA1c were 139.35 mg, 218 mg and 6.81% implying a better glycemic control. Out of 200 eyes, 85 had tear film break up time less than 10 seconds, while 115 eyes had more than 10 seconds. And majority of eyes with poor glycemic control had positive TBUT result. Out of 200 eyes, 62 had showed staining with rose Bengal with score 4 or more, while 110 eyes had no stains or a score of less than 4. The mean HbA1c levels of patients having a positive rose Bengal test was 9.14 while of those with negative results was much lower 7.05. Out of 200 eyes, 68 had showed staining with fluorescein, while 132 eyes had no stains or less than 5 corneal spots. The mean HbA1c levels of patients having a positive rose Bengal test was 8.7 while of those with negative results was much lower 7.2. Out of 200 eyes examined, 117 did not show any metaplasia, while 54 showed grade 1 changes, 23 showed grade 2 changes and only 6 showed grade 3 changes.

Table 1: Retinopathy, HbA1c levels and schirmer's test

Variables		Schirmer score 15+	Schirmer score 10-15	Schirmer score 5-10	Schirmer score Below 5
HBA1C	Less than 7%	43	12	5	2
	7.1-8.0%	26	30	20	11
	8.1-9.0%	4	5	17	7
	More than 9%	0	10	9	12
	P value	0.001*			
Retinopathy	No	65	42	32	15
	Mild NPDR	3	8	11	5
	Moderate NPDR	0	6	7	6
	Severe NPDR	0	0	0	5
	PDR	0	0	0	5
	P value	0.02*			

*indicates statistically significance at p≤0.05

Table 2: Rose Bengal test, TBUT, and HbA1c levels

TBUT					Rose Bengal Test			
HBA1C	Positive	Negative	Total	P value	Positive	Negative	Total	P value
Less than 7%	6	52	58	0.001*	0	58	58	0.03*
7.1-8.0%	30	52	82		13	69	82	
8.1-9.0%	24	6	30		22	8	30	
More than 9%	30	0	30		30	0	30	
Total	90	110	200		65	135	200	

*indicates statistically significance at p≤0.05

Table 3: Fluorescein test, Impression cytology and HbA1c levels

Fluorescein test					Impression cytology			
HBA1C	Positive	Negative	Total	P value	Positive	Negative	Total	P value
Less than 7%	6	52	58	0.001*	0	58	58	0.03*
7.1-8.0%	30	52	82		13	69	82	
8.1-9.0%	24	6	30		22	8	30	
More than 9%	30	0	30		30	0	30	
Total	90	110	200		65	135	200	

*indicates statistically significance at p≤0.05

Discussion

Dry eye syndrome (DES) is very common among the general population with 28% of the adult patients [24]. The discomforts of dry eye patient may have burning sensation, foreign body sensation, stickiness, watering, red eye, and blurring of vision. It may give rise to ocular complications such as keratoepitheliopathy and keratitis.

There exists a considerable discrepancy between the subjective complaints of patients and the clinical tests available to assess dry eye. It is difficult to correlate test results of TMH, TBUT, SchT in clinical trials. Each form of dry eye has certain global features which include ocular surface damage, reduced tear hyperosmolarity and tear film stability. Diagnosis of dry eye depends on patients' symptoms, 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 of 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.

The prevalence of dry eye in this study was found to be 47.90%. The studies on diabetic patients showed increased prevalence of dry eye like Manaviat *et al.* [25] showed 54% of those with diabetes had dry eye while Hom and De Land1 [3] did a study on patients with either diabetes or borderline diabetes and found that 53% of patients presented with dry eye. But our findings differ from that of Kaiserman *et al.* [26] (20.6% prevalence) as they determined DED by ocular lubrication use.

The mean age was 52.10 years. The prevalence of dry eye was found to significantly increase with increase in age of the patients. This finding was statistically significant and corresponds to the study by Moss *et al.* [27] which showed an association between older age and an increase in dry eye symptoms. We found a higher prevalence of dry eye in women, compared to men, but the difference was statistically not significant. This finding has corresponded to the findings of other studies. Moss *et al.* [27] found a prevalence of 16.7% in women compared to 11.4% in men. Sahai *et al.* [28] found prevalence of 22.8% in women compared to 14.9% in men in his study on hospital based population.

In our study, as per the OSDI score we found 52.01% did not have dry eye, 31.9% eyes had mild dry eye and 11.09% moderate dry eye while 5% eyes had severe dry eye. This is similar to Ibtesam Nasimul Hasan *et al.* [29] who did a study in India in 2014 and also matching the data reported by study conducted by Aggarwal *et al.* [30]. Our observations are in line with previous studies elsewhere, which have shown a positive correlation between OSDI scores and glycemic control. K Divya *et al.* [31] in their study conducted in India on 2016-2017 also found positive correlation between OSDI Score and HbA1clevels in study population. S. Kan *et al.* [32] in their study in Turkey in 2016 concluded that diabetes appears to cause elevation in OSDI score and increase in Tear Film Osmolarity level, especially if blood glucose is poorly regulated.

In our study we find that with increase in HbA1c levels the Schirmer values decreases. That means there is an inverse correlation between glycemic control and Schirmer test values. This finding is in correlation with most of the studies in the past some of which include study by Goebbels *et al.* [33] Dogru M *et al.* [34] Ozdemir M *et al.* [35] Gupta I *et al.* [36] and Divya K *et al.* [31] all of these studies has reported that Schirmer test values decrease in diabetic patients more so in patients with poor glycemic control.

In our study we find that patients with advanced stages of retinopathy had higher chances of developing dry eye. This finding was statistically significant and is in line with studies conducted in the past. Studies by J. Nepp *et al.* [37] R. L. McKown *et al.* [38] Ozdemir M *et al.* [35] and Zhang X *et al.* [39] have demonstrated a positive correlation between retinopathy and dry eye.

Conclusion

In the present study, we find a significant correlation between the prevalence of dry eye in the diabetic patient which shows poor glycemic control is directly related to dry eye. Our result provides evidence that DM is associated with increased DES. This study reveals that attention should also be paid on dry eye, particularly among patients suffering from DM when they are concerned about diabetic retinopathy. Obviously, this study is limited to this extent; further prospective studies on large-scale assessment are needed to confirm the association between DES and DM.

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Conflict of interest: None declared

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