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Ocular surface disorder among adult patients with type II diabetes mellitus and its correlation with tear film markers: A pilot study

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Abstract:

PURPOSE: The purpose is to study the ocular surface changes among patients with diabetes mellitus (DM) and to correlate them with tear film markers such as insulin-like growth factor (IGF)-1, interleukin (IL)-1β, and tumor necrosis factor (TNF)-α levels.

MATERIALS AND METHODS: The study was carried out on diabetic patients (>5 years' duration) and healthy age- and gender-matched controls with 21 individuals in each group. Schirmer's test for basal and reflex tear secretion, tear film breakup time (TBUT) for tear stability, ocular staining score (OSS) for dryness severity, ocular surface disease index (OSDI) for symptomatic assessment of dryness and conjunctival impression cytology (IC) for epithelial cell integrity, keratinization, squamous metaplasia, and goblet cell density was studied. Thirty microliters of tears were collected to test IGF-1, IL-1β, and TNF-α levels.

RESULTS: Patients with DM showed significantly low Schirmer's, TBUT, and OSS values than controls. OSDI score showed moderate-severe dryness in patients with DM and only mild symptoms among controls. An abnormal IC score was seen among cases and controls. The level of TNF-α was significantly increased in patients with DM and positively correlated with Schirmer and TBUT values ($P < 0.05$).

CONCLUSION: Dry eye is more prevalent in patients with DM compared to controls as evidenced by poor OSDI score, Schirmer, TBUT, and OSS. TNF-α in the tears of patients with DM is a useful marker that showed a good correlation with Schirmer, TBUT, and dry eye symptoms. IC could not conclusively differentiate the dry eye status in patients with DM from controls.

Keywords:

Diabetes mellitus, dry eye disease, ocular surface, tear film markers

Introduction

Ocular surface abnormalities are common in patients with diabetes mellitus (DM) who have an increased risk of developing dry eye disease (DED), corneal epithelial fragility, decreased corneal sensitivity, abnormal wound healing, and increased susceptibility to infected corneal ulceration.[1,2] Around 47%–64% of patients with DM had keratopathies in their lifetime.[2] Furthermore, ocular surface changes correlated with the duration of the disease, poorly controlled serum glucose level, peripheral neuropathy, and proliferative diabetic retinopathy.[3-5]

It is well known that patients with DM exhibit reduced corneal sensitivity, which is thought to have a negative effect on reflex tear secretion. Reduced goblet cell density in the conjunctiva along with meibomian gland dysfunction accounts for the reduced tear break-up time seen in these individuals.[6,7] It is also proposed that longstanding disease

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may cause damage to the microvascular supply to the lacrimal gland, impairing lacrimation.[8,9]

Low tear production or excessive evaporation increases tear osmolarity which can further lead to the release of inflammatory mediators. A meta-analysis has shown that elevated levels of inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-10, interferon-α, γ, and tumor necrosis factor (TNF)-α are found in tears of patients with DED.[10,11] Liu *et al*. identified elevated levels of EGF to differentiate diabetic from nondiabetic dry eye, which correlated with corneal fluorescein staining and Schirmer's test.[12] In previous studies, the IL-1β and TNF-α levels were increased in conjunctival biopsy specimens in diabetic patients with dry eye and tear TNF-α levels correlated with the severity of diabetic retinopathy.[13,14]

Ocular surface changes in patients with DM is interesting, not yet fully explored topic and the correlation between the severities of these disorders with tear film markers is less known. Considering the key role of the markers and the scope of this study, we choose insulin-like growth factor (IGF)-1, IL-1β, and TNF-α to correlate the functional and pathological changes on the ocular surface in patients with DM and identify potential biomarkers for the pathogenesis of DED in diabetes.

Methods

This cross-sectional comparative study was performed after obtaining informed consent from each participant and study protocols were reviewed and approved by the institutional ethics committee (approval number: PGRMC 24/10/2016).

Patient involvement

Patients were not involved in the research development such as study designing and recruitment and the results were not disseminated to the participants.

Study procedure

Cases included were patients with preexisting type II DM (Group 1) who attended the outpatient department for diabetic retinopathy screening from July 2016 to December 2017. Age- and gender-matched healthy adults willing to participate in the study were enrolled as controls (Group 2). Patients with preexisting autoimmune disease, renal failure, contact lens wear, ocular allergy, long-term topical medications, and ocular surgery were excluded from the study. A diagnosis of uncontrolled diabetes was made if the fasting blood glucose ≥126 mg/dl on two separate occasions or random blood sugar ≥200 mg/dl with symptoms or postprandial 2-h plasma glucose ≥200 mg/dl, using the criteria given by the American diabetes association.[9] Ocular surface disease index (OSDI) questionnaire was given to both the patients and healthy controls for symptomatic assessment of dryness of eyes. A score of 0–12 was normal, 13–22 was defined as mild symptoms, 23–32 as moderate, and 33–100 as severe. Individuals were subjected to tear film tests including Schirmer's test and tear film break-up time (TBUT). Ocular staining score (OSS) for each eye was calculated using the summation of fluorescein score for the cornea and lissamine green scores for the nasal and temporal bulbar conjunctiva. OSS with value >3 was taken as abnormal. Conjunctival impression cytology (IC) was obtained using nitrocellulose acetate filter paper strips (0.22 μ pore size). To perform the test, eyes were anesthetized with topical anesthesia (0.5% proparacaine hydrochloride) and a filter paper of 5 × 10 mm size was applied on superotemporal bulbar conjunctiva of the subject with the help of a blunt forceps. A cotton bud was used to gently press on the paper, and it was removed in a peeling motion after 2–3 s and placed in a container with a fixative containing rectified spirit. The strips were stained using periodic acid–Schiff and Papanicolaou and graded by a single-blinded experienced pathologist based on epithelial cell integrity, squamous cell metaplasia, epithelial keratinization, goblet cell density, and presence or absence of inflammatory cells. The total IC score was calculated by adding the score of both eyes and the sum was analyzed among cases and controls. Subscore analysis of 5 parameters of the worse eye was studied using the individual scores for each parameter (given as 0, 1, 2) based on the severity. Thirty microliters of pooled basal tears were collected a-traumatically from the inferior meniscus of the right and left eye using a 10 μl micropipette tip attached to a plastic pipette. Care was taken to minimize reflex tearing. Tear samples were taken into 0.5 ml Eppendorf tubes and transferred to an icepack to carry it to a freezer for storage area at −70°C until use. ELISA testing of IGF-1, IL-1β, TNF-α was done using RAY BIO® 96-well microplate Human ELISA kits according to the manufacturer's instruction and all standards were within limits of detection.

Data were entered into a computerized database and analyze during the SPSS version 19.0, IBM corporation, Chicago, United States for Windows version 19.0. Continuous variables are reported as mean with standard deviation and categorical data are displayed as frequencies with percentages in parentheses. The normality distribution of the variables was analyzed using Kolmogorov–Smirnov's test and Schirmer 1, Schirmer 2, total IC score, TNF-α were found to be normally distributed. Tear film breakup time, OSS, IL1-β, and IGF-1 were found to be nonnormally distributed. For correlation analysis of normative variables, Pearson's correlation was used. $P \leq 0.05$ was considered statistically significant. To determine

the statistical significance of group differences among the study groups for continuous data following normal distribution independent *t*-test was done, for data not following normal distribution Mann–Whitney's test was used. Chi-square test was used to assess the relationship between categorical variables.

Results

Demographic and clinical characteristics

The study population included 42 individuals, 21 in each group. Both groups were well matched for age and gender [Table 1]. In Group 1 (diabetes group), 10 patients had more than 10 years' duration of DM, 12 patients had uncontrolled blood sugars and 11 patients had proliferative diabetic retinopathy [Table 1]. In Group 1, 16 patients (76.2%) had moderate-to-severe dry eye symptoms and Group 2 had most of the patients (90.5%) with normal to mild dry eye symptoms based on OSDI. The average OSDI score was 42.95 ± 17.38 and 16.75 ± 5.45 in cases and controls, respectively. Group 1 patients had a lower Schirmer I, Schirmer 2, TBUT, and poorer OSS which was statistically significant ($P < 0.01$) [Tables 2 and 3]. IC showed loss of epithelial integrity, reduced goblet cells, and squamous metaplasia in both the groups. The total IC score was abnormal in 13 patients (61.9%) in the diabetes group and 11 patients (52.38%) in the control group. The average Total IC score was 11.00 ± 6.4958 in the diabetic group and 06 ± 5.00 in the control group, which was not statistically significant ($P = 0.126$).

Tear film marker insulin-like growth factor-1, interleukin-1β, and tumor necrosis factor-α levels

The median value of tear IGF-1 in the diabetic group was 3.71 ng/mL, three times elevated compared to controls which was 1.26 ng/mL. This difference was not statistically significant ($P = 0.085$). Median value of IL1-β was similar in both groups, 0.78 pg/mL in diabetics compared to controls which was 0.74 pg/mL ($P = 0.772$).

In our study, the mean value of TNF-α in cases was 437.03 pg/ml compared to controls which was 310.68 pg/ml. This difference in value among both groups was found to be statistically significant ($P = 0.047$).

Pearson's correlation of tumor necrosis factor-α with dry eye parameters

A bivariate correlation analysis was done to find a correlation between the statistically significant elevated tear film marker TNF-α and dryness parameters. There was a moderate correlation between tear TNF-α levels with Schirmer 1 ($r = 0.552$), Schirmer 2 ($r = 0.446$) and TBUT ($r = 0.548$) among cases which was statistically significant ($P < 0.05$). There is a negative correlation between TNF-α and OSS but it was found to be statistically not significant [Table 4].

Table 1: Characteristics of study subjects in both groups

Variable	Cases	Controls
Number of subjects	21	21
NPDR	10	
PDR	11	
Age (years), mean±SD	54.59±11.58	51.33±10.683
Gender (male/female)	19/2	19/2
Number of patients with duration of DM >10 years	10	0
Number of patients with uncontrolled blood sugars	12	0
Fasting blood sugar (mg/dL), mean±SD	183.39±72.8	
Postprandial blood sugar (mg/dL), mean±SD	361.2±85.22	

SD=Standard deviation, PDR=Proliferative diabetic retinopathy, NPDR=Non-PDR

Table 2: Comparison of variables among cases and controls

Variable	Mean±SD		*P* (independent *t*-test)
	Cases	Controls	
Normative data			
OSDI	42.95±17.38	16.75±5.45	<0.01
Schirmer 1 (mm)	9.57±9.330	22.57±6.794	<0.01
Schirmer 2 (mm)	5.52±7.026	14.43±5.671	<0.01
Total IC score	11.00±6.4958	06±5.00	0.126
TNF-α (pg/mL)	437.03±231.66	310.68±160.90	0.047
Variable	**Median (minimum-maximum)**		***P* (Mann-Whitney's test)**
	Cases	**Controls**	
Nonnormative data			
TBUT (s)	3.00 (2.00-10.00)	10.00 (7.00-10.00)	<0.01
OSS	2.00 (0.00-6.00)	0.00 (0.00-1.00)	<0.01
IGF 1 (ng/mL)	3.71 (0.56-46)	1.26 (0.385-12.49)	0.085
IL-1β (pg/mL)	0.78 (0.29-13.77)	0.74 (0.19-9.53)	0.772

OSS=Ocular staining score; TBUT=Tear film breakup time; IC=Impression cytology, TNF=Tumor necrosis factor, OSDI=Ocular surface disease index, SD=Standard deviation

Discussion

Dry eye disease is multifactorial, characterized by unstable tear film causing a variety of symptoms, visual impairment, and potentially accompanied by ocular surface damage. Tear film abnormalities in patients with DM occur due to poor quantity and quality of tears, combined with a subnormal ocular surface.[15-18] In this study, Group 1 patients had a higher OSDI score and a significantly lower mean Schirmer, TBUT, and abnormal OSS value compared to controls. Patients with proliferative diabetic retinopathy had more severe symptoms of DED and higher OSS

Table 3: Mean values of includes epithelial cell integrity, squamous cell metaplasia in terms of nucleus cytoplasmic ratio, epithelial keratinization, goblet cell density

Variable	Mean ±SD		*P*
	Cases	Controls	
Epithelial cell integrity	1.67±0.577	1.38±0.954	0.724
Squamous metaplasia	1.33±0.577	1.12±0.769	1.00
Degree of keratinization	1.33±0.577	1.06±0.736	1.00
Goblet cell density	2.00±1.00	1.76±0.955	1.00
Total IC score	11.00±6.4958	06±5.00	0.126

P value was not found to be significant. IC=Impression cytology

Table 4: Pearson's correlation of tumor necrosis factor - with dry eye parameters

Variable	Cases (*r*)	*P*
Schirmer 1	0.552	<0.01
Schirmer 2	0.446	0.043
OSS	−0.485	0.26
TBUT	0.548	0.01
Total IC score	0.250	0.318

OSS=Ocular staining score; TBUT=Tear film breakup time; IC=Impression cytology

consistent with other studies.[19,20] IC showed loss of epithelial integrity, reduced goblet cells, and squamous metaplasia. There is accumulating evidence that inflammation is one of the key components of dry eye and pro-inflammatory cytokines are increased in the tear fluid from patients with DED.[21] Diabetes plays a crucial role by inducing microvasculopathy, neuropathy, and tear hyperosmolarity over the ocular surface stimulating a cascade of inflammatory events that subsequently cause lacrimal function unit dysfunction.[22,23] The inflammatory mediators destroy the goblet cells leading to reduced mucin production and tear film instability which in turn causes increased evaporation and a vicious cycle of tear hyperosmolarity.[24] In our study analysis of tear film markers showed elevated levels of IGF-1 in the diabetes group which was not statistically significant ($P = 0.085$). The study did not show any tear elevation of IL 1-β levels in the diabetes group. Tear TNF-α levels were higher in the diabetes group which was statistically significant ($P = 0.047$) and showed a positive Pearson's correlation with dry eye parameters such as Schirmer 1, Schirmer 2, TBUT, and total IC score. Previous studies have shown that the dry eye severity correlates well with the squamous metaplasia on conjunctival and corneal IC.[6] The squamous metaplasia detected could be attributed to a primary surface disease, conjunctival hypoxia, or metabolic alterations of the conjunctival epithelial cells independent of tear film abnormalities.[25,26] Although our study shows abnormal IC score in cases, the difference was not found to be statistically significant ($P = 0.126$). This could probably be due to aging and exposure to ultraviolet rays due to agricultural work among the males, which is a risk present in both groups in our patient population. Dogru *et al*. demonstrated squamous metaplasia and low goblet cell density in diabetic patients and suggested that peripheral neuropathy and poor metabolic control are important determinants of diabetic ocular surface disease.[27] However, our study did not evaluate the corneal sensitivity or fluctuations in metabolic control in these patients. Hyperglycemia involves the expression of the inflammatory cytokines of the innate immune system, such as TNF-α and IL 1-β, which are clearly involved in lacrimal gland impairment in other animal and human models.[15,28] Both insulin and IGF-1 receptors in the human ocular surface have been identified previously, and IGF-1 used to treat neurotrophic keratopathy.[29,30] Wu *et al*. observed that an increase in IGF binding protein in human tears attenuated IGF-1 receptor signaling in the diabetic cornea which may contribute to epithelial compromise and the pathogenesis of ocular surface complications reported in diabetes.[31] Diabetic dry eye can be attributable to inflammatory etiology and TNF-α in the tears of patients with DM is a useful marker that showed good correlation with dry eye symptoms, Schirmer's test, and TBUT. This result implies that proper inhibition of TNF-α may lead to the improvement of DED which has shown promising results in murine models.[32]

Strengths and limitations of the study

Our study is the first to correlate the level of tear film markers such as IGF-1, IL-1β, and TNF-α with dry eye parameters. We used the modified IC scoring to include several parameters such as nuclear-cytoplasmic ratio, squamous metaplasia, goblet cell density, epithelial keratinization, presence or absence of inflammatory cells but a small sample size could not establish a significant association between dryness severity and IC changes in patients with DM when compared with the normal population. Corneal sensitivity was not studied which may have an important role in the pathogenesis of DED in diabetes.

Conclusion

Dry eye is more prevalent in patients with DM when compared to age and gender-matched nondiabetic population as evidenced by poor OSDI score Schirmer, TBUT, OSS, and elevated inflammatory cytokines. Patients with proliferative diabetic retinopathy have more symptoms of dry eye and higher OSS. IC could not conclusively differentiate the dry eye status in cases compared to controls. Early screening and diagnosis of dry eye in diabetic patients especially those with uncontrolled blood sugars or presence of diabetic retinopathy is essential for the treatment of dry eye, to prevent corneal erosions and secondary infections which if left untreated may lead to visual impairment.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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