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ORIGINAL RESEARCH

Dry eye disease in type 2 diabetes mellitus: association with diabetic retinopathy and neuropathy

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ABSTRACT

Aim- To study the prevalence of dry eye disease(DED) and its association with diabetic retinopathy (DR), diabetic neuropathy (DN) and other metabolic parameters in patients with type 2 diabetes mellitus. Materials and methods- Dry eye disease was assessed in 102 patients with type 2 diabetes mellitus using OSDI (Ocular Surface Disease Index) score, tear break up time(TBUT) test and Schirmer's test. All the subjects underwent indirect ophthalmoscopy, DN screening was done based on Revised NDS score, DR was graded according to Early Treatment Diabetic Retinopathy (ETDRS) criteria. The relation of DED with status of diabetic retinopathy, peripheral neuropathy, dyslipidemia, metabolic control and duration of disease was also assessed. Results- The prevalence of dry eye disease was 37.2%.We observed a significant associationof dry eye disease with diabetic retinopathy (p=0.017) and diabetic neuropathy(p=0.019). Conclusion- As the prevalence of DED among diabetics is high and diabetic retinopathy and neuropathy are often found to be associated with DED, therefore, along with screening for DR and DN, assessment of dry eyes should be routinely included in patients with diabetes in ophthalmology clinics.

Keywords- Diabetes mellitus,dry eye disease, diabetic retinopathy, diabetic neuropathy.

Introduction:
Diabetes Mellitus (DM) is presently one of the leading causes of non communicable disease related deaths worldwide. Currently,the prevalence of diabetes in India is estimated to be nearly 70 million.[1] While diabetic retinopathy (DR) and diabetic cataracts are well-known ocular complications, dry eye disease (DED), also referred to askeratoconjunctivitissicca, is also common among diabetics. Studies have reported the prevalence of DED to be as high as 54% in diabetes.[2] DED is defined as an abnormality in the qualityor quantity of tears or in tear dynamics due to anycause, resulting in ocular discomfort, visual disturbance,decreased tear film stability, and potential damage to theocular surface.[2]Damage to the microvasculature of the lacrimal gland accompanied by autonomic neuropathy might impair tear secretion in patients with long term diabetes.[3,4]Manaviat*et al*. found that DED was significantly associated with duration of diabetes and diabetic retinopathy.[2]Patients with diabetic retinopathy do not often complain of symptoms of dry eye, but they have pathological and clinical signs of DED.[5] Peripheral neuropathy in diabetic patients has been postulated as a causal factor for abnormal tear secretion [3],though Najafi*et al*.[6] reported no significant correlation between DED and DN. Effects of hyperglycemia on any component of the LFU may be transferred to the entire system via neural connections, leading to inadequate tear production or excessive tear loss, abnormalities in blinking, and changes in tear film composition causing DED.[7] In severe DED, tear film dysfunction aggravates the ocular surface, which induces a corneal epithelial defect, leading to secondary bacterial infection, corneal ulcers leading to visual impairment.[8]Thus, early diagnosis and treatment of dry eye is essential to avoid such complications. The relationship and association of complications of diabetes like diabetic retinopathy and diabetic neuropathy with DED is not well documented in India. Keeping this in mind, the present study was done to assess dry eye syndrome in patients with type 2 diabetes andexplore any association of DED with DR with DN.

Materials and methods
Study design:
A cross-sectional hospital based study consisting of 102 diabetic patients attending diabetes clinic in our hospital was undertaken to study dry eye disease(DED) in type 2 DM patients and its relationship with diabetic retinopathy and diabetic neuropathy.

Inclusion criteria:
Adults over 30 years of age of either sex diagnosed to have type 2 DM who were willing to participate in the study were included.

Exclusion criteria:
Patients who have undergone any ocular surgery in the past six months, contact lens users, patients on local or systemic medication which are known to cause dry eye such as topical antiglaucoma medications, antihypertensive medications, oral contraceptive pills, patients with other ocular surface disease and systemic disease which are known to cause dry eye other than diabetic mellitus such as various autoimmune diseases, parkinsonism, lupus and thyroid disorders,pregnant women and smokers were excluded from the study.

Method of Data Collection:
Written informed consent was obtained from all subjects and the research had the approval of the institutional review board and ethics committee and was carried out in accordance with the Declaration of Helsinki. Detailed history regarding duration of diabetes and treatment was taken. Data regarding dry eye was collected in terms of age, sex, presenting symptoms, duration, progression, and associated conditions. All study participants completed the Ocular Surface Disease Index (OSDI; Allergan, Inc., Irvine, CA, USA) questionnaire to score dry eye symptoms. The OSDI consists of 12 questions based on symptoms within the past 1 week. Brief general systemic examination was done. Revised NDS(neuropathy disablility score) was used to screen for diabetic peripheral neuropathy (Diabetes Research & Center, 2000); a score ≥6 points on a 10 point scale was defined as neuropathy. Blood samples were sent to laboratory for assessment of fasting blood sugar, postprandial blood sugar, glycosylated haemoglobin(HbA1c) and serum lipid profile. Participants with total cholesterol≥ 240mg/dl or high density lipoprotein< 40mg/dl or low-density lipoprotein ≥160mg/dl or triglycerides≥200mg/dl were defined as having dyslipidemia.

Ophthalmological Examination:
Ophthalmic examination was carried out by assessing the visual acuity with Snellens chart, detailed anterior segment examination with slit-lamp to assess the condition of eyelid, meibomian gland, conjunctiva and cornea.Evaluation of the ocular surface and tear film was done by performing tear film break up time (TBUT) test and Schirmer's I test (under topical anesthesia). TBUT value <10secs and Schirmer's test value <10mm was taken as abnormal. Clinical evaluations were done on both eyes, and the mean of the two eyes was used for analysis. Since there is no international diagnostic standard for DED, in our study, diagnosis was established by OSDI score>12 along with positivity of one or both the tests(TBUT and Schirmer's I test).Detailed fundus examination was done under indirect ophthalmoscopy under mydriasis with 0.5% tropicamideeyedrop. Retinopathy, if present was classified as per Early Treatment of Diabetic Retinopathy Study such as non-proliferative diabetic retinopathy (NPDR), mild, moderate, and severe NPDR and PDR.

Statistical analysis:
IBM-SPSS version 26 was used for statistical analysis.Results on continuous measurements are presented on mean ± standard deviation and results on categorical measurements are presented in number (%).The chi-square test, independent paired t test and Pearson correlation analyses were performed. A p value < 0.05 wasaccepted as statistically significant.

Results
In our study, 102 patients with type 2 diabetes were assessed. The subjects (66 males, 36 females) ranged in age from 31 to 81years. Out of 102 patients,38 patients (37.3%) had dry eye disease(DED). DED was observed in 34.8% males and 41.6% females. Prevalence of DED was 37.9% among patients ≤55years of age and 36.4% among those >55years. Mean duration of diabetes in our patients was 5.41±6.19years. Prevalence of DED was 34.4% in patients with <5years of diabetes,37.3% in patients with 5-<10years and 44% in patients with ≥10years duration of diabetes. Mean HbA1c(glycated hemoglobin) level of our patients was 8.95±2.12%. Mean Schirmer's value and TBUT value was significantly lower (p<0.001 and p<0.001

respectively) among patients with DED, while mean OSDI score was significantly higher compared to patients without DED(p<0.001). However, there was no significant association of DED with age(p=0.517), gender(p=0.501),duration of diabetes(p=0.199), HbA1c(p=0.197), type of treatment(OGLD vs insulin)(p=0.192) and components of lipid profile(p>0.05).(Table 1).
Prevalence of DED was significantly higher in patients with DR(59%) than without DR(31.2%)(p=0.017). DR was observed in 21.5% of our patients. 9.3%(n=6) had mild NPDR,7.8%(n=5) had moderate NPDR, 7.8%(n=5) had severe NPDR and 9.3%(n=6) had PDR. Association of DED with DR was significant (p=0.017), but no significant association with grades of retinopathy (p=0.791) was observed.(Table 2).DED was significantly more prevalent among patients with DN(46.6%) than without DN(23.8%)(p=0.019). DED was more among patients with dyslipidemia (45%) than those without(26.1%), but association between them was not significant(p=0.054).(table1).

Table1 : Demographic and clinical characteristics of DED and non DED subjects among 102 diabetic patients

Factors	**DED (n=38)**	**Non DED (n=64)**	***P* value**
Age (years)	54.97±10.02	53.59±10.55	0.517
Gender (Male/Female)	23/15	43/21	0.501
Duration of DM(years)	6.43±7.17	4.80±5.49	0.199
OSDI(score)	55.25±33.06	16.01±23.61	<0.001
Schirmers (mm)	7.39±3.74	18.56±5.17	<0.001
TBUT(s)	5.42±2.37	13.63±2.05	<0.001
Fasting blood glucose (mg/dl)	126.26±42.79	132.58±55.04	0.546
Postprandial blood glucose (mg/dl)	212.05±67.34	210.89±88.60	0.945
HbA1c(%)	9.31±2.31	8.74±1.99	0.197
Type of treatment (OGLD/Insulin)	28/10	54/10	0.192
Total cholesterol(mg/dl)	171±45.61	167.53±38.06	0.681
Triglyceride (mg/dl)	174.11±93.97	180.91±87.63	0.713
HDL(mg/dl)	41.95±7.28	45.23±9.69	0.074
LDL(mg/dl)	86.37±24.32	85.58±25.54	0.878
Diabetic retinopathy(DR) (present/absent)	13/25	9/55	0.017
Diabetic neuropathy(DN) (present/absent)	28/10	32/32	0.019
Diabetic dyslipidemia(DL) (present/absent)	27/11	33/31	0.054

Table 2: Prevalence of DED among patients with different grades of DR

Grades of DR	**DED (n=38)**		**Non DED (n=64)**		***P* value**
	n	(%)	n	(%)	
No DR	25	(65.78)	55	(85.93)	
Mild NPDR	4	(10.52)	2	(3.12)	
Moderate NPDR	3	(7.89)	2	(3.12)	
Severe NPDR	2	(5.26)	3	(4.68)	
PDR	4	(10.52)	2	(3.12)	*P*=0.791

Discussion

Various studies have reported the prevalence of DED among diabetics ranging from 17.5% to 54.5%.[2,6,9-15] Prevalence of DED was 37.2% among type 2 diabetics in our study. Seifart*et al*.[9] found prevalence of dry eyes to be 52.8% among those with type 1 and type2 diabetes and 9.3% among the normal control subjects. In a retrospective review of 400 patients with dry eyes by Jain *et al*,[12] 80 (20%) patients had diabetes indicating diabetes to be a common systemic illness associated with DED. By direct measurement by tear lab osmolarity system, Najafi*et al*. [6] found prevalence of dry eyes to be 27.7 % among diabetics.Yazdani*et al*,[13] reported DED to be more prevalent among DM2 patients than those with DM1 (55% and 27% respectively, *P*=0.001).In a community-based study including 1360 subjects,the prevalence of dry eye diseasewas lower(17.5%) than that observed in hospital-based studies.[14]This wide range of variation in prevalence of DED in diabetics may be due the different methods used for diagnosisamong the studies varying from diagnosis based only on symptoms to diagnosis based on tear film osmolarity measurement. Also the climatic conditions of the region may affect prevalence of dry eyes among the subjects.Community based studies [14] reported lower prevalencecompared to hospital based studies due to poor glycemic control among those attending hospital.

Age, sex, duration of diabetes and glycatedhaemoglobin

Though prevalence of dry eyes is reportedly more among females of higher age group than males due to menopause, such a phenomenon may be neutralized due to diabetes among diabetics. DED among female diabetics was higher in our study, but was not significant. Similarly, as age increases, due to tear film instability and alteration in lipid composition of tears, the incidence of dry eyes increases but no significant association of age with DED was seen in our patients. Various other studies have reported no significant association of DED with age and gender.[2,6,13,15] Few studies,[2,15]have reported increase in DED with increase in duration of diabetes while some other studies,[6,14]reported no significant association between the two. Mean duration of diabetes in our study population was less than others,[2,15] which may be the reason behind no significant association between the two in among our subjects.There was no significant relation of DED with the type of treatment(OGLD vs insulin)our patients were undergoing, similar to report by Najafi*et al*.[6] and Nepp*et al*.[16] Studies found positive correlation of dry eyes with HbA1c.[14,15,17] However, we didn't observe any significant

relation between the two, similar to report by Yazdani*et* al.[13]Divya K *et al*.[15]reported positive correlation between HbA1c and OSDI score and inverse correlation between HbA1c and TBUT values similar to our study but in our study the association were not significant($p<0.05$). However, mean OSDI score was found to be more among non diabetics than diabetics in a study by Beckman *et al*.[18]

Dry eye and diabetic retinopathy, neuropathy and dyslipidemia

Prevalence of DR in our study was 21.5%, similar to Chennai Urban Rural Epidemiology Study (CURES)(22%).[20]Several studies have reported that patients with diabetic retinopathy had a higher chance of having TBUT<10 seconds and Schirmers value<10mm than those without diabetic retinopathy.[3,17,21,22] Significant association between DED and DR was seen in our study(p=0.017). Khurana*et al*.[23] found that patients with DR had 6.5times more chances ofsuffering from DED than patients without DR. All the stages of DR were nearly equally prevalent in our study and no significant association between DED and severity of DR was observed, unlike other studies.[6,16,17]Najafi*et al* stated that patients with DR are more prone to develop DED(specially PDR and CSME), which is not true for diabetic neuropathy(DN) and nephropathy.

However in our study, prevalence of DED in patients with DN was significantly higher than those without DN. Dogru et al showed that diabetic patients with peripheral neuropathy and poor metabolic control have lower tear film tests values as compared to controls.[3]Nerve fibers play an important role in the maintenance of normal function of the cornea and the integrity of the LFU. DED is particularly common in patients with Type 2 diabetes complicated with polyneuropathy (PN). Impaired corneal neurons and reduced corneal sensitivity have been reported in diabetic patients with PN.[24] Long term uncontrolled diabetes may lead to impaired corneal sensations and result in lack of symptoms of dry eye resulting in lower OSDI score as was reported among patients with longer duration of diabetes in a hospital based study.[2]

Elevated cholesterol levels is known to cause lipid concentration alteration in tear film of eye resulting in tear film instability and dry eyes. Several studies found significant association between DED and dyslipidemia.[25,26] Many studies have studied the association of DR with diabetic dyslipidemia,[27] and a conclusive link still remains elusive,but,no studies so far have evaluated the prevalence of dyslipidemia with DED among diabetics.DED was more prevalent among our patients with dyslipidemia but the association was not significant.

Limitations

Our study has few limitations. We had not performed tear film osmolarity assessment which is an objective test for the diagnosis and follow-up of DED as its not a widely used diagnostic tool in a developing country like India. However, test combination of OSDI/Schirmer test/TFBUT has been shown to have an accuracy of 99.3% for the diagnosis of DED.[4] Small sample size and conduct of the study as a cross sectional study at a single site are other potential limitations of the study. Lack of control group is another limitation in our study. Corneal sensation could not be assessed due to lack of access to corneal aesthesiometry. Further studies on large samples with control group with the inclusion of tests such as corneal esthesiometry and tear osmolarity, will provide valuable insight into the potential mechanisms and treatment options for diabetic DED.

Conclusion

DED is a common complication of diabetes, which is often neglected. Its possibility should be kept in mind while dealing cases with diabetes in our clinics. Since both DR and DN is associated with higher prevalence of DED, and patients with DR mostly have associated features of neuropathy, therefore, any case with DR should be assessed for DED and referred for neuropathy assessment and needful to prevent avoidable blindness.

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