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DRY EYES IN DIABETES MELLITUS PATIENTS AND ITS ASSOCIATION WITH DIABETIC RETINOPATHY

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Abstract

Background: India, with the highest number of diabetics, has become the diabetic capital of the world. Diabetes can lead to various complications in various organs of our body, including the eyes. It can affect all aspects and parts of our eyes which includes ocular surface abnormalities that can cause dry eyes. The present study was undertaken to evaluate the amount of tear production, the stability of the tear film and the condition of the ocular surface in diabetic individuals in order to detect possible tear film abnormalities and to evaluate the various risk factors for dry eyes. Furthermore, an attempt was made to find any correlation between diabetic retinopathy and dry eyes. Aim: To study the prevalence of dry eyes in diabetes mellitus patients and correlate the dry eye status with the stages of diabetic retinopathy. Methods: 150 diabetic patients visiting the eye out-patient department (OPD) were subjected to a comprehensive ophthalmic evaluation, including visual acuity assessment, slit lamp evaluation, fundoscopy and tests for dry eyes which comprised of a questionnaire, meibomian gland status, tear meniscus height, fluorescein staining of cornea, tear film break-up time (TBUT) and Schirmer's test. Chi-square and Fisher Exact test was used to compare mean values, find P-values, and ensuring statistical significance. The Statistical software namely SPSS 11.0 and Systat 8.0 were used for data analysis. Results: Among 150 participants, 88 (58.7%) were males and 62 (41.3%) were females. Average mean age was 42.27 years. Association of dry eyes with glycemic control and diabetic retinopathy was found to be statistically significant while gender, duration of diabetes, and random blood sugar did not have any significant association with dry eyes. Conclusion: Diabetes and dry eyes appear to be a common association. Reduction in the modifiable risk factors of dry eye is essential to reduce its prevalence. Examination for dry eyes should be an integral part of the assessment of diabetic eye disease.

Keywords: Dry Eye Disease, Diabetic Retinopathy, Glycemic Control.

INTRODUCTION

Diabetes Mellitus (DM) has topped the leading health related catastrophes the world ever witnessed.[1] By 2040, the prevalence of diabetics globally would raise to 642 million.[2] India leads the world in diabetic population and estimated to have 62.4 million people with diabetes, and 77.2 million with prediabetes.[3] It is predicted that by 2030, in India, DM may affect up to 79.4 million.[4] Hence WHO has labeled India as the diabetic capital of the world. The total health burden due to DM is mainly due to its complications in different organs. Diabetic retinopathy (DR) affects more than 93

million people worldwide.[5] Various corneal components like the epithelium, endothelium, and nerves etc., are also affected by diabetes. Just as diabetic retinopathy stands as a marker of more generalized microvascular disease, corneal neuropathy can act as a tool to predict peripheral and autonomic neuropathy, and hence gives an opportunity for early treatment. In addition, diabetic complications have been recognized in cornea as indicated by alterations of immune cells in cornea. Furthermore, it causes both quantitative and qualitative abnormalities in tear secretion, decreased corneal sensitivity and poor adhesion of regenerating epithelial cells.

All these imply a widespread disease of the ocular surface due to diabetes including common diseases like dry eye, recurrent corneal erosions to severe complications like corneal ulcerations, superficial punctate keratopathy and persistent epithelial defects. Close monitoring of diabetic patients as well as glycemic control is important for the prevention of dry eyes. Early diagnosis of dry eye syndrome in diabetic patients is important for improving the ocular surface and quality of vision.[6]

The present study was undertaken to evaluate the amount of tear production, the stability of the tear film and the condition of the ocular surface in diabetic individuals in order to detect possible tear film abnormalities and to evaluate the various risk factors attributable to dry eye. Furthermore, an attempt was made to find any correlation between diabetic retinopathy and dry eyes.

MATERIALS AND METHODS

Design and Setting

This was a cross-sectional hospital based clinical study of 150 diabetic patients to investigate the prevalence of dry eyes and its correlation relationship with diabetic retinopathy in patients who presented to the department of ophthalmology, Sharda hospital, Greater Noida between July 2019 to January 2021.

Inclusion criteria:

All patients of either sex, in all age groups, diagnosed to have diabetes mellitus (by endocrinologists/ as per ADA criteria) of any duration.

Exclusion criteria:

1. Patients with systemic diseases and local ocular disease/surface abnormalities (other than diabetes mellitus) which are known to cause dry eyes/ocular surface abnormalities.
2. Patients who are chronic contact lens wearer.
3. Patients who have undergone ocular surgeries in the past.
4. Patients on local or systemic medications, which are known to cause dry eyes/ocular surface disorders.

Study Tool

After taking informed consent, detailed history, which included a questionnaire about dry eye, and a detailed ocular evaluation was performed.

A validated questionnaire of ocular symptoms relating to dry eye was used which included the following questions: [7]

1. Do your eyes ever feel dry?
2. Do you ever feel a gritty or sandy sensation in your eye?
3. Do your eyes ever have a burning sensation?
4. Are your eyes ever become red?
5. Do your eyes ever feel sticky?
6. Do your eyes ever feel watery or teary?
7. Do you notice much crusting on your lashes?
8. Do your eyes ever get stuck shut?

Presence of symptoms from the dry eye questionnaire was further graded as rarely (at least once in 3–4 months), sometimes (once in 2–4 weeks), often (at least once a week), or all the time. Presence of one or more symptoms often or all the time was taken as positive.

A brief general and systemic examination was carried out followed by a detailed ocular examination that included recording visual acuity with Snellen's chart, anterior segment examination under slit lamp, intraocular pressure with applanation tonometry and fundus examination with both indirect ophthalmoscopy and 90D slit lamp biomicroscopy. Retinopathy if present was classified as Mild Non-Proliferative Diabetic Retinopathy (NPDR), Moderate NPDR, Severe NPDR, Proliferative Diabetic Retinopathy (PDR) and High risk PDR.

Meibomian gland status was graded as follows: [7]

Grade 0-no disease

Grade 1-plugging with translucent serous secretion when compressing the lid margin

Grade 2-plugging with viscous or waxy white secretion when compressing the lid margin

Grade 3- plugging with no secretion when compressing the lid margin.

Cornea was evaluated in detail for its sheen, surface (superficial punctate keratitis SPK/mucous plaques/filamentary keratitis). Corneal sensation was tested with a fine moist cotton wisp and graded as normal, reduced or absent.

Dry eye assessment:

Tear meniscus height was recorded as normal or low (under slit lamp, thin beam)

Precorneal tear film was observed for presence of debris (mucous/oil droplets/debris)

Tear film break-up time (TBUT): A dry fluorescein strip was touched to the inferior fornix with the patient looking up. The patient was instructed to blink once or twice and then stare straight ahead without blinking. The cornea was scanned under low slit lamp magnification using a blue cobalt filtered light. The time of appearance of the first dry spot formation (small black spots within the blue-green field) from the last blink was recorded. Values <10 seconds were taken as abnormal.[7]

Fluorescein staining of cornea was graded from 0-3 as:

0 – No staining of corneal epithelial surface.

1 – Mild staining occupying < 1/3 of corneal epithelial surface.

2 – Moderate staining occupying < ½ of corneal epithelial surface.

3 – Severe staining of > ½ of the corneal epithelial surface.

Schirmer's test: It was performed by placing a precut strip of Whatman filter paper No. 41 inbetween the medial 2/3rd and lateral 1/3rd of the inferior cul-de-sac of the patient and the amount of wetting of the paper strip after 5 minutes was measured. Wetting of ≤10 mm was taken as abnormal.

Dry eye was graded into three types-mild, moderate, and severe.

Mild dry eye: Schirmer's test reading of less than 10 mm in 5 minutes, TBUT less than 10 seconds and less than one quadrant of staining of the cornea.

Moderate dry eye: Schirmer's test reading of 5 to 10 mm in 5 minutes, TBUT of 5 to 10 seconds with punctuate staining of one to two quadrants of the cornea.

Severe dry eye: Schirmer's test reading of less than 5 mm in 5 minutes, TBUT of less than 5 seconds with punctuate staining of more than two quadrants of the cornea.

Chi-square and Fisher's exact test has been used to find the significance of association of various symptoms, signs, risk factors etc., with the prevalence of dry eyes. Odds Ratio (OR) has been used to find the strength of relationship between symptoms, signs, risk factors with prevalence of dry eyes. Student's t-test has been used to find significance difference of FBS and PPBS between dry eyes and no dry eyes. The diagnostic statistics viz., sensitivity, specificity, PPV, NPV, Accuracy and Kappa have been used to find the diagnostic values of the screening tests.

Statistical software: The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

A total of 150 diabetic patients participated in the study of which 50 (33.3%) were type I diabetes and 100 (66.6%) were type II diabetes with the mean being 42.27 years. 58.7% of the study population was males while 41.3% were females.

29.9% subjects reported at least one of the eight dry eye symptoms often or all the time, of these 23.33% had dry eyes which was found to be statistically significant (table 1). Presence of clinical signs of dry eye in diabetic patients was also found to be statistically significant (table 2).

Overall prevalence of dry eyes in the study was 36%. The prevalence was 15.02% in type I while in type II it was 38%. Duration of diabetes was not statistically associated with the prevalence of dry eyes. Glycemic control of diabetes was found to have a strong association with the incidence of dry eyes (table 3). Also**,** there was statistically significant association between retinopathy and dry eyes (table 4).

Table 1: Prevalence of Symptoms in Participants of this Study and Association of Each Dry Eye Symptom with dry eyes.

Symptoms (Questionnaire) (n=150)	Total (%)	Dry eyes (%)	P value
Eye feel Dry	18 (12.0)	17 (11.3)	<0.001
Gritty feeling	21 (14.0)	20 (13.3)	<0.001
Burning Sensation	41 (27.3)	37 (24.7)	<0.001
Stickiness	8 (5.3)	8 (5.3)	<0.001
Watering	13 (8.7)	11 (7.3)	<0.001
Redness	11 (7.3)	7 (4.7)	0.051
Crusting	2 (1.3)	1 (0.7)	0.067
Eyes getting stuck	13 (8.7)	12 (8.0)	<0.001

Table 2: Clinical Signs of Dry Eyes in Type I and Type II Patients.

Signs	Type I (n=50)	Type II (n=100)	Total (n=150)
Low Tear Meniscus	10 (20.0%)	23 (23.0%)	33 (22.0%)
Abnormal Precorneal tear film	10 (20.0%)	23 (23.0%)	33 (22.0%)
Conjunctival abnormalities	14 (28.0%)	36 (36.0%)	50 (33.3%)
Dull Cornea	9 (18.0%)	28 (28.0%)	37 (24.7%)
SPK	2 (4.0%)	18 (18.0%)	20 (13.3%1)

Table 3: Comparison of the Mean FBS and PPBS levels in Diabetics with and Without Dry Eyes

Glycemic control	No dry eyes (n=96)	Dry Eyes (n=54)	P value
FBS in mg/dl	138.84±57.78	178.63 ±70.26	<0.001
PPBS in mg/dl	190.58 ± 77.69	252.37±92.51	<0.001

Table 4: Association of Diabetic Retinopathy with Dry Eyes

Retinopathy (n=150)	Total (%)	Dry eyes (%)	P value
No retinopathy	105 (70.0)	25 (23.8)	0.484
Mild NPDR	18 (12.0)	8 (44.5)	0.691
Moderate NPDR	14 (9.3)	11 (78.5)	0.047
Severe NPDR	4 (2.6)	3 (75)	0.032
PDR	8 (5.3)	6 (75)	0.023
High risk PDR	1 (0.7)	1(100)	<0.001
Inference	Retinopathy is not statistically associated with the incidence of dry eyes (P>0.05)		

DISCUSSION

In present study, prevalence of dry eyes was found to be 36% (type I diabetes - 32%, and type II - 38%). Prevalence of dry eyes in diabetes reported by various studies compared with the current study shows wide disparity, varying from 18.1% to 70% (Table 5). Much of this disparity stems from the fact that there is no standardization of the types of patients selected for the study, dry eye questionnaires, objective tests and dry eye diagnostic criteria.

Table 5: Comparison of the Prevalence of Dry Eyes in Various Studies

S. NO.	STUDY	YEAR	PREVALENCE IN DIABETICS	PREVALENCE IN NON-DIABETICS
1	Seifart et al[8]	1994	57% in type I and 70% in type II	-
2	Moss et al[9]	2000	18.1%	14.1%
3	Nepp et al[10]	2000	43%	-
4	Martin Goebbels[11]	2000	37% in type I	-
5	Inoue et al[12]	2001	22.8%	8.5%
6	Peponis et al[13]	2002	37%	-
7	Beaver Dam study[14]	2004	19.8% in type II	13.9%
8	Kaiserman et al[15]	2005	20.6%	-
9	Najafi et al[16]	2013	27.7% in type II	-
10	Elsaadani et al[17]	2014	18%	-
11	Shah et al[18]	2015	67%	-
12	Aljarousha et al[19]	2016	15.9%	13.6%
13	Ribeiro et al[20]	2016	26.2%	-
14	Present study		32% in type I and 38% in type II	-

Moss et al reported a higher incidence of dry eyes in diabetic women (16.7% compared with 11.4% in men). In the present study, 21.3% of dry eye patients were males and 14.7% were females. It is 2.2 times more for males in type I diabetics (p=0.213) and 1.37 times more for females in Type II diabetics (P=0.449).

However, the prevalence of dry eyes was not statistically associated with sex when both Type I & Type II were combined. Deficient tear secretion from estrogen deficiency in menopausal women has been hypothesized to explain sex differences, although studies have found that women on hormone replacement therapy may have an increased risk of dry eye[21].

In the present study, age did not influence the prevalence of dry eyes in type I patients. Duration of diabetes was not statistically associated with the prevalence of dry eyes in type I but was significantly associated with the prevalence of dry eyes in type II (P=0.022) with OR=2.65 indicating that incidence of dry eyes is 2.65 times more for >10 years of diabetes in type II diabetes.

Binder et al reported that dry eye symptoms affected some type 1 diabetic patients only during the hyperglycemic phases. This could result from high extracellular fluid osmolarity disturbing tear production, rather than representing a chronic complication of diabetes. Significantly elevated FBS and PPBS levels were found to be associated with dry eyes, indicating some role of hyperglycemia.

A few previous studies have also correlated glycemic control and keratoconjunctivitis sicca (KCS). In diabetic patients suffering from KCS, poorer glycemic control (higher mean annual HbA1c levels) led to a higher annual consumption of ocular lubrication, regardless of age.[22] Moreover, in a multivariate analysis, glycemic control was an independent factor in forecasting consumption of ocular lubrication.

Comparable findings were reported by Seifart et al[8], Nepp et al[10] showed that the severity of KCS correlated with the severity of diabetic retinopathy, which is well known to correlate with glycemic control. Blepharitis and meibomitis are well known to contribute to evaporative dry eyes.

Diabetic patients are prone to develop these more often. There is a possibility that, in some patients, meibomitis may create sufficient conjunctival inflammation to decrease tear secretion by damaging accessory lacrimal gland tissue in the conjunctiva.[23] In the

present study 9 patients had blepharitis out of which 3 had dry eyes, meibomitis was present in 16 patients of which 12 had dry eyes. Corneal sensation recording in the present study was a subjective method, total 25 patients had reduced corneal sensation of which 22 had dry eyes.

10 of our patients had history of laser treatment (PRP) in the past, 4 had dry eyes. Reduction in corneal sensitivity is a known diabetic complication. Corneal sensitivity is decreased in proportion to both the duration of the disease and the severity of the retinopathy.[4]

The decrease in sensitivity of the cornea in diabetic retinopathy patients and reduction in sensitivity after laser photocoagulation.[10,11] The diminished sensitivity may be a kind of diabetic neuropathy. This can lead to the reduction of stimulatory signals from the ocular surface to the lacrimal gland and the influence on regulatory systems. Hypertension was present in 24 type II patients, of these 11 patients were diagnosed with dry eyes. Diabetic hypertensives were 1.63 times more likely to develop dry eyes.

Though it is not a known risk factor for dry eyes, association could be of mere coincidence or could be due to medications taken for hypertension mainly beta blockers. In our study total number of symptom positive patient was 44 (29.3%), of these 35(23.3%) had clinical signs and tests positive for dry eyes. The diabetic patients may exhibit dry eye signs with or without discomfort due to corneal neuropathy.[11] Tear film instability may be a result of either tear deficiency or evaporative dry eye.[8]

One of the common objective tests used to make diagnosis of dry eye is tear break up time (TBUT). In the present study TBUT was found to be ≤10 sec. in 32% (48 /150). Many type I patients (10%) had TBUT between 5-10 seconds with no other abnormality.

In present study, the total tear secretion (measured by Schirmer's test) was ≤10 mm in 22% of the study population. Basal secretion rate was slightly less affected than total secretion. Thus, the present data suggest that the amount of reflex tearing is more affected in diabetics. It is possible that the decreased amount of reflex tearing in diabetics may be the result of a diminished corneal and conjunctival sensitivity, which has been demonstrated in diabetics by electronic aesthesiometry.[24]

In the present study, a strong statistically significant association was found between retinopathy and dry eyes ($p<0.001$) which was in agreement with the study conducted by Nepp et al[10] that correlated severity of retinopathy with the severity of dry eyes. Further studies thus are needed to further clarify association between diabetic retinopathy and dry eyes.

CONCLUSION

Diabetes and dry eyes appear to be a common association. Predominantly, milder grade of dry eye was seen in type I diabetics and mild to moderate in type II diabetes patients. Higher prevalence of asymptomatic tear film instability was noted in type I patients. Corneal hypoesthesia was strongly associated with dry eyes in diabetics. Significant association has been found in glycemic control in diabetics and diabetic retinopathy with dry eye. Reduction in the modifiable risk factors of dry eye is essential to reduce its prevalence. Therefore, examination for dry eyes should be an integral part of the assessment of diabetic eye disease.

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Conflicts of Interest: There are no conflicts of interest

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