Case Control Study to Evaluate Tear Film Function and Ocular Surface Disorder in Diabetic Patients

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ABSTRACT

BACKGROUND
Diabetic retinopathy and early development of cataracts are well-known ocular complications of long-standing diabetes. In recent years various researchers have reported ocular surface disorders, particularly dry eyes in diabetic patients which if left untreated may result in a variety of corneal complications. These ocular surface disorders can be clinically diagnosed by performing a detailed slit lamp examination, Schirmer’s test and tear film break-up time. Our study intended at assessing tear film and ocular surface disorders in diabetic patients and study tear film function in them and compare it with non-diabetic patients.

METHODS
A comparative cross-sectional study was done on 100 diabetic and 100 non-diabetic patients > 30 years of age visiting OPD of health centre of tertiary care hospital of Central India. Clinical data and detailed clinical history were obtained from all subjects through direct patient interviews and reviewing of their medical records followed by a comprehensive ocular examination that included best-corrected vision, slit lamp examination, and Tear Film break up time (TBUT) & Schirmer test.

RESULTS
In our study, mean TBUT was found to be significantly reduced in diabetics (15.94 ± 3.8) as compared to non-diabetics (20.13 ± 6.6). No significant difference was found in the Schirmer test reading between diabetics (17.13 ± 3.20) and non-diabetics (19.20 ± 6.23). Diabetic male patients had significantly decreased mean TBUT & mean Schirmer test readings as compared to diabetic females. Mean Schirmer reading & Mean TBUT were lowest in a patients having > 20 years of DM and highest in patients having < 5 years of DM. No positive correlation was found between HbA1c (Glycosylated Haemoglobin) and diabetic retinopathy with TBUT/Schirmer test readings.

CONCLUSIONS
Our study showed that the tear film stability was found to be affected in diabetic patients, as compared to non-diabetic subjects as evident by the lower level of TBUT in diabetic patients. Significantly reduced TBUT with no significant difference in Schirmer test reading in diabetic as compared to non-diabetic subjects might be due to a decrease in basal secretion with normal overall tear secretion. The absence of subjective symptoms of dryness in spite of decreased TBUT in the diabetic group might be due to a decrease in corneal sensitivity caused by diabetic peripheral neuropathy in diabetic patients. There was an increase in the prevalence of DES with an increasing duration of DM. Rheumatoid arthritis was found to be a risk factor for DES. Diabetic males were found to be at risk for developing dry eye syndrome. Hence it can be concluded from our study that every diabetic patient should undergo a comprehensive eye examination which should include various tests for dry eye assessing multiple tear parameters.

KEY WORDS
Schirmer Test Reading, Tear Film Break Up Time, Dry Eye Syndrome, Diabetes Mellitus, Glycosylated Haemoglobin.
Diabetes is one of the most common leading causes of blindness in the 20–70 years of age group. The major microvascular complications of diabetes include peripheral neuropathy, nephropathy, and diabetic retinopathy. Some of the well-known ocular complications of diabetes mellitus include cataracts, glaucoma, and recurrent corneal abrasions.[1,2] Ocular surface disorders particularly dry eyes have been recently reported by some researchers. Dry Eye Syndrome (DES) also known as keratoconjunctivitis sicca (KCS) means dryness of the cornea and conjunctiva.[3] Dry eye syndrome is one in which there is either qualitative or quantitative reduction in tear production. Insufficient tear production results in aqueous deficient dry eye disorder. Hyper-evaporative dry eye disorder is due to excessive tear loss which is usually associated with infections, infrequent blinking and other factors.[4] An estimated world population of 25–30 million is experiencing ocular discomfort due to dry eyes.[5,6] Yun J et al. reported that 54.3% of diabetics suffer from dry eyes. The occurrence of dry eye disease in the United States was found to be 14.6%. It is more prevalent in middle age women of >50 years due to autoimmune aetiology and in older age groups.[9] Edward K et al. reported older age group, female gender, diseases like collagen vascular diseases, diabetes mellitus, hepatitis C infection, vitamin A deficiency, androgen insufficiency, procedures like refractive surgery of the cornea, hematopoietic stem cell transplantation, postmenopausal estrogen treatment, irradiation, drugs like antiarrhythmics, selective serotonin reuptake inhibitors, tricyclic antidepressants, diuretics and beta-blockers as risk factors for dry eye.[10]

Dry eye syndrome is a multifactorial disease involving tears and the ocular surface. DES results in tear film instability which has the potential to damage the ocular surface and cause symptoms of ocular discomfort & visual disturbances. There will be an increase in the osmolarity of the tear film and ocular surface inflammation in dry eyes.[11] The pathogenesis of dry eye involves stress to the ocular surface that can be from a change in environmental conditions, antigens exposure, infection, endogenous stress, or genetic factors resulting in the release of pro-inflammatory cytokines, matrix metalloproteinases and chemokines that will activate the autoreactive helper T cells which will infiltrate the lacrimal gland and ocular surface[12,13] resulting in pathological inflammation and damage to the ocular surface.[14] Punctuate keratopathy, trophic ulceration, and persistent epithelial defects are among some of the corneal complications which patients with dry eyes may suffer if left undiagnosed and untreated which adversely affects their vision-related quality of life.[15]

Various studies have shown a high prevalence of dry eye ranging between 27.7% - 54.3% in diabetes mellitus.[16-25] There are varieties of the mechanism through which diabetes mellitus can lead to dry eye.[16,17] Diabetic neuropathy, metabolic dysfunction, or lacrimal gland dysfunction are some of the implications of diabetes mellitus that may contribute to the development of dry eyes.[26-28] Patients suffering from dry eyes have a variety of ocular symptoms like burning, itching, redness, pain, ocular fatigue, blurred vision, and reduced contrast sensitivity which often affects daily activities such as reading, watching television and driving which in turn will adversely affect the vision-related quality of life.[29-31]

The clinical diagnosis of dry eye is an OPD-based procedure involving slit-lamp examination, Schirmer’s test, tear film break-up time and Rose Bengal staining. There are many studies done in the past to assess dry eye and ocular surface disorders in diabetes, but the results remain controversial. This study was done to assess the tear film functions and ocular surface disorder in diabetic patients and comparative evaluation with age-matched non-diabetic patients attending the out-patient health center of a tertiary care hospital in Central India.

### METHODS

A comparative cross-sectional study was undertaken at the health centre of super specialty hospital in Central India after taking permission from Institutional Ethical Committee. Patients visiting OPD of the health centre of super specialty hospital were among the registered cohort of patients of Bhopal gas tragedy, 100 diabetic and 100 non-diabetic patients of >30 years of age and were selected by simple random sampling.

Demographic data including the age and sex of all patients were noted. Detailed clinical history was taken by direct patient interview and reviewing their medical records which included the duration of diabetes as well as a history of other diseases, history of addiction, family history of diabetes, treatment history, exposure to excessive sun rays, computer use, use of air conditioner, contact lens use, Lasik surgery, allergies, Sjogren’s syndrome, rheumatoid arthritis, Parkinson, lupus, some medications such as antihistamines, tricyclic antidepressants, oral contraceptives, and drugs used to treat high blood pressure and diuretics.

Every study participant had undergone a detailed ocular examination by recording best-corrected vision, slit lamp examination, Tear Film break up time (TBUT) and Schirmer test by ophthalmologist and optometrist. Slit-lamp examination was done to examine tear meniscus, tear film for the presence of debris & mucoid flakes, lids to look for meibomianitis, blepharitis, sty etc, cornea to look for filaments, mucus plaques.

Tear Film break-up time (TBUT) was performed after instilling fluorescein dye into the conjunctival sac followed by several blinks. A broad beam of cobalt blue light was used to examine the tear film. TBUT was noted as the time interval between the last blink and the appearance of black spots or lines around the central cornea. Schirmer’s test was performed without prior instillation of topical xylocaine 4% with the help of Whatman’s filter paper strip of size 5 mm by 35 mm. A filter paper strip was inserted between the middle and outer third of the lower lid after folding 5 mm from one end of the filter paper strip and patients were allowed to blink in between as necessary. The readings were noted after 5 minutes as the distance of wetting from the folded end.

### Statistical Analysis

Statistical analysis was done by using the SPSS version 20 programme. The chi-square test was used for comparing and
calculating the P-value. All data were expressed as Mean ± SD. Appropriate statistical tests were applied as necessary. A p-value of less than 0.05 was considered significant.

**RESULTS**

In the present study, there was more number of males in the diabetic group as compared to the non-diabetic group but the difference was not statistically significant. (P-value = 0.0875). In the diabetic group, the maximum number of patients was in the age group 60 - 65 years (26 %) whereas in the non-diabetic group it was 50-54 years (24 %).

The mean age in the diabetic group was 57.8 ± 10.59 and in the non-diabetic group 53.72 ± 9.12 (P-value = 0.003) which is statistically significant. There was more number of elderly patients in the diabetic group as compared to the non-diabetic group.

In diabetic group, majority of patients had duration of diabetes mellitus < 5 yrs (42 %) followed by 5 - 9 yrs (26 %) & 10-14 yrs (17 %). Associated hypertension was found in 69 % of patients and coronary artery disease (CAD) in 3% of patients in the diabetic group in contrast to the non-diabetic subjects group where only 33 % had associated hypertension and 3 % CAD. This difference is statistically significant (P-value <.0001).

The mean TBUT reading was significantly less (p-value = 0.018) in the diabetic group (15.94 sec ± 3.848) as compared to the non-diabetic group (17.13 sec ± 3.20), although there was no significant difference between the two groups in Schirmer’s test readings. [Table 1]

In both groups, Schirmer test readings and TBUT were found to be more in females as compared to males and in the diabetic group, it was significantly higher. [Table 2]

In the diabetic group, the mean Schirmer value & mean TBUT (16.65 ± 3.99) were highest in patients having a duration of DM < 5 years and the lowest mean Schirmer value (18.75 ± 1.76) and mean TBUT (13.5 ± 3.53) in patients having >20 yrs of DM. The difference was not statistically significant. [Table 3]

In both groups, the mean Schirmer value & mean TBUT were highest in patients in the age group of 40 – 44 years. In the diabetic group, lowest Schirmer test reading and mean TBUT were found in patients < 40 years of the age group who was documented case of rheumatoid arthritis followed by patients in the age group > 65 years of age. In the non-diabetic subjects group, lowest mean Schirmer value (17.14 ± 6.78) & mean TBUT (14.78 ± 3.74) were found in patients in the age group of 60 – 65 years. [Table 4] The difference is not statistically significant.

The highest mean HbA1c (8.66 ± 2.91) was found in diabetic patients having a Schirmer test reading of 5 - 9 mm and a mean duration of DM 4.51 ± 4.62 years. The lowest mean HbA1c was found in diabetic patients having a Schirmer test reading < 5 mm and a mean duration of DM 8 years. [Table 5]

The highest mean HbA1c (8.54 ± 2.67) was found in diabetic patients having TBUT < 10 sec, a mean age of 61.14 ± 16.07 years & mean duration of DM 6.44 ± 5.81 years. The lowest mean HbA1c (7.77 ± 1.95) was found in diabetic patients having TBUT >10 -15 sec, a mean age of 63.18 ± 8.21 years and a mean duration of DM 77.26 ± 6.06 years. The maximum number of diabetic patients having diabetic retinopathy (8 eyes of 4 patients) were having Schirmer test reading 15 – 19 sec [Table 5].

The majority of patients in the diabetic (57 %) and non-diabetic (59 %) group were addicted to either smoking,
tobacco chewing and alcohol intake alone or in a combination of them.

**DISCUSSION**

Diabetes mellitus is a systemic disease and has an impact on various organs of the body by causing micro and macrovascular changes. It affects ocular surface integrity mainly through microcirculation changes through various mechanisms.[32]

In this study, the mean TBUT test readings were significantly reduced in the diabetic group (15.94 ± 3.84 sec) as compared to the non-diabetic group (17.13 ± 3.20 sec) p-value = 0.0184; this finding correlates with various studies conducted in previous years and had reported the effect of diabetes on tear film stability.[31,34,35] The study conducted by Jin et al. showed that TBUT was reduced in type II diabetes as compared to the normal healthy non-diabetic subject.[36]

Schirmer test is used to quantify the amount of tear production mainly aqueous layer. No significant statistical difference was found in the present study in mean Schirmer readings between diabetic and non-diabetic subjects (p-value = 0.08).

Again, this finding is similar to some previous studies that showed diabetic patients might have normal overall tear production as evident by normal Schirmer test findings and decreased TBUT is a decrease in basal tear secretion.[33] On the contrary, Goebel’s study reported that tearing reflex as evident by decreased Schirmer test reading was significantly reduced in diabetic patients as compared with the non-diabetic group.[37]

Jain et al. in their study reviewed 400 patients with dry eyes referred to a tertiary referral centre and found diabetes in 20% of patients and hence identified diabetes as a risk factor for dry eye.[38] Another study conducted on 50 diabetics and 50 non-diabetic patients of age 50–70 years reported lower values of tear secretion & TBUT in diabetics as compared with non-diabetic healthy subjects.[39]

In both the diabetic and non-diabetic group, the mean Schirmer value & mean TBUT were highest in patients in the age group of 40 – 44 years. In the diabetic group, lowest Schirmer test reading and TBUT were found in patient <40 years of the age group who was documented case of rheumatoid arthritis followed by patients in the age group > 65 years of age. In the non-diabetic group, the lowest mean Schirmer value & mean TBUT was found in a patient in the age group 60 – 65 years. Rheumatoid arthritis was identified as a risk factor for dry eye disease. The possible mechanism might be an abnormal immune system producing antibodies against self-antigens in ocular tissues leading to ocular manifestations of DES.[40]

In both diabetic and non-diabetic group, Schirmer test readings and TBUT were found to be lower in patients with age > 65 years as compared to subjects of age group < 40 years but values were not statistically significant.

The mean age in the diabetic group (57.80 ± 10.59) was significantly higher as compared to the non-diabetic group (53.72 ± 9.12) P-value = 0.003. There were more elderly patients in the diabetic group as compared to the non-diabetic group which can be a confounding factor but as on comparison no significant statistical difference was found in Schirmer test readings between diabetic and non-diabetic groups but TBUT was found to be significantly lower in diabetic subjects group.

Hence age does not seem to be a confounding factor in our study.

Further, more detailed studies with a large sample size should be designed to rule out the effect of age on tear film quality and quantity.

In the diabetic group, absence of subjective symptoms of dryness (as no patients had reported dry eye symptoms) despite lower values of TBUT might be the result of masking of dry eye symptoms due to the associated decrease in corneal sensitivity caused by diabetic peripheral neuropathy.

Many published studies showed a correlation between dry eye with the duration of diabetes and severity of retinopathy;[41,42] however, some other studies showed that metabolic control might have a greater impact than the duration of diabetes.[43,44]

In the diabetic group, majority of patients had a duration of diabetes mellitus < 5 yrs (42 %) followed by 5-9 yrs (26 %) & 10-14 yrs (17 %). In both groups, the mean Schirmer value and TBUT were highest in patients having a duration of DM < 5 years and lowest in patients having > 20 yrs of DM. Hence it can be concluded that there is a decrease in tear production and an increase in the probability of occurrence of dry eye diseases with increasing duration of DM which also correspond to previous studies.

The mean Hba1c was highest in diabetic patients having a Mean Schirmer test reading of 5 – 9 mm & TBUT < 10 sec and lowest in diabetic patients having a Mean Schirmer test reading of < 5 & TBUT 10 -15 sec. No positive correlation was found between Hba1c & TBUT/ Schirmer test reading. This might be due to the fact as long-term metabolic control cannot be assessed by a single Hba1c reading as it can only help to assess the blood sugar level of last 3 months.

In both diabetic and non-diabetic groups, it was noted that Schirmer test readings were significantly lower in males as compared to females. Further detailed studies might be needed to find whether this difference is due to circulating sex hormones or is merely a gender difference. Some studies had reported the effect of decreased circulating sex hormones in postmenopausal diabetic females on ocular surface integrity resulting in dry eye, a thing that might add to the severity of the condition.[32]

14 eyes of 8 diabetic patients having diabetic retinopathy had Schirmer test readings in the range of 15 – 24 mm and 4 eyes of 3 diabetic patients had Schirmer test readings < 15 mm. 15 eyes of 8 diabetic patients having diabetic retinopathy had TBUT in the range of 16 – 20 sec and 5 eyes of 4 diabetic patients had TBUT < 15 sec. No positive correlation was found between diabetic retinopathy & Schirmer test reading/ TBUT. This might be due to different pathophysiology of occurrence of dry eye and diabetic retinopathy. This finding is different from the study done by Riordan-Eva et al. who reported that dry eye was more in diabetic patients with diabetic retinopathy.[39]

In the diabetic group, 69 % of patients had associated hypertension & coronary artery disease (CAD) in contrast to the non-diabetic group 33 % which is statically significant (P-value < .0001). Hence it can be concluded that there were more comorbidities associated with DM that can further
affect microvasculature that was already compromised because of diabetes or vice versa.

The majority of patients in the diabetic and non-diabetic groups were addicted to either smoking, tobacco chewing and alcohol intake alone or in a combination of them. Further studies need to be done to correlate the effect of addiction on the health of individuals and with various systemic diseases.

**CONCLUSIONS**

There are limited epidemiological studies that had studied the prevalence of dry eye syndrome among diabetic patients; some studies have revealed a positive correlation between diabetes mellitus and dry eye syndrome.[45,46,47]

Our study concluded that the integrity of tear film was affected in diabetics as compared to non-diabetic patients. The limitation of our study was the small sample size.

The tear film stability in our study was found to be affected in diabetic patients, as compared to non-diabetic subjects as evident by a significantly lower level of TBUT in diabetic patients. Diabetic male patients had significantly decreased Schirmer test readings and TIBUT as compared to females and hence are at higher risk of developing Dry Eye Syndrome. The absence of subjective symptoms of dryness despite low values of TBUT in the diabetic group may be attributed to decreased corneal sensation due to diabetic peripheral neuropathy or lifestyle changes made by diabetic patients after diagnosis.

The connective tissue disorder was found to be a risk factor for dry eye syndrome with both decreased TBUT and Schirmer test readings.

Multiple factors are involved in the pathophysiology of the development of the dry eye in diabetes. The measurement of multiple tear parameters is necessary for diagnosing dry eye in diabetic patients as all the parameters are not affected in a similar pattern. Hence it can be concluded from our study that every diabetic patient should undergo a comprehensive eye examination which should include tests for dry eye.

We believe that our study findings will pave the way for further large multicentric prospective studies which will further help to plan strategies for the management of dry eye in diabetic patients and will also develop awareness in the general population especially diabetic patients, regarding measures to avoid the occurrence of dry eye syndrome.

**REFERENCES**


