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Original Article

Correlation of Impression Cytology and Tear Film Status with The Metabolic Control and Duration of Type 2 Diabetes Mellitus

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Abstract

Purpose: *To determine whether changes in conjunctival epithelial morphology and the tear film dysfunction in type 2 Diabetes mellitus is related to its metabolic control or duration.*

Materials and Methods: *A cross sectional clinical study which includes 200 patients of type 2 Diabetes mellitus. The patients demographic details, Conjunctival impression cytology (CIC)which was done using Ultipor Nylon filter paper ,Tear film break up time(TBUT) and Schirmer's test I & II were evaluated.*

Results: *The percentage of the study population with abnormal changes in conjunctival morphology was 44.4% in those with less than 10 years of duration and 73.9% in those with more than 10 years duration of diabetes mellitus. The association between HbA1C and CIC shows that 34.3% of good control and 66.7% of poor metabolic control had changes in conjunctival epithelial morphology , which is statistically significant. The prevalence of tear film instability was 79% among type 2 Diabetes mellitus. Tear film dysfunction in less than 10 years of diabetes were found as 75% and in 86.1% for more than 10 years .Nearly 70% patients of good metabolic control and 86.3% patients of poor control had tear film instability, which was statistically significant.*

Conclusion: *Changes in conjunctival morphology was correlating significantly with both increase in duration and poor metabolic control whereas Tear film instability was found to be more significantly associated in patients with poor metabolic control than with its duration.*

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Keywords : *Conjunctival Morphology, Diabetes Mellitus, Metabolic Control, Tear Film Instability, Duration Of Diabetes.*

Introduction

Diabetes mellitus is a group of metabolic disease characterized by hyperglycaemia, resulting in defect in insulin action, secretion or both. Diabetes is Greek word means" to pass through" and mellitus is a Latin word for "honey" (Referred to as sweetness). Diabetes mellitus can lead to various ocular complications such as diabetic retinopathy (DR), cataract, glaucoma, keratopathy, refractive changes, oculomotor nerve palsy, infections and chronic eyelid inflammation. Dry eye is a common ocular surface disorder affecting 6.9-10.6% of the adult population.[1] Dry eye is a disorder of precorneal tearfilm deficiency or excessive evaporation, which present with symptoms like ocular discomfort Untreated dry eye may lead to corneal complications like corneal ulceration, persistent epitheliopathy and superficial punctuate keratopathy. The vicious cycle of dryness, decrease in goblet cells, conjunctival keratinization and further dryness is termed the "Ocular Surface Disorder" cycle. In a patient, if symptoms of dry eye are unaccompanied by any gross ocular disease, the condition is called 'Discomfort Eye Syndrome' (DES). Studies have shown that there is prevalence of 54% of individuals with or without symptoms of DES among diabetes.[2]

There has been minimal research regarding the ocular surface changes in Diabetic patients in relation to their clinical parameters. This study has investigated the changes of ocular surface and tear film by CIC ,Schirmer test 1&2, tear break up time, in type 2 Diabetes mellitus and also has attempted to correlate whether the changes in tear film and ocular surface is due to duration or poor metabolic control.

Subjects and Methods

The study was done for a period of one year in the Department of Ophthalmology after obtaining Institute Ethical Clearance and informed written consent from the participants. It is a cross sectional clinical study of 200 patients of type 2 Diabetes mellitus aged more than 30 years. Patients who had history of drug abuse, contact lens wear, topical medication, ocular surgery within the previous 3 months, patients with secondary ocular and systemic disease (except hypertension) were excluded from the study.

Detailed history including duration of diabetes, assosiation with hypertension, type of treatment like Insulin or Oral Hypoglycemic agents was taken. Meanwhile, FBS/ PPBS/ HbA1C values are done and noted for correlation. Detailed ocular examination was done using slit lamp biomicroscope. Conditions of lid meibomian gland, conjunctival and corneal surface was examined.

Tear film status evaluation was done first was TBUT (tear breakup time). No anesthetic eye drops was instilled. A presterilized dry flourescein strip was placed for a second in the inferior fornix of conjunctiva while the patient is asked to look upwards. The cornea was examined with wide slit and cobalt blue filter in slitlamp biomicroscope. The time of appearance of the first random dry spot or break (black spot in the blue green field) from the last blink was measured as TBUT. Next, Schirmer's test 1and 2(reflex and basal tearing respectively) was checked. For Schirmer's test 1, tear test strip (a pre- cut strip of Whatman filter paper measuring 5×35mm) was placed in the inferior conjunctival cul-de-

sac and the patient was made to sit in the dark room. The amount of wetting on the tear test strip was measured, followed by Schirmer's test 2, where, after instillation of topical anesthetic eye drop (4% Xylocaine) and the test strip paper was placed for five minutes and the amount of wetting is measure. IMPRESSION CYTOLOGY OF CONJUNCTIVA was done by instilling the anesthetic eye drop (4% xylocaine), wire speculum was placed in the eye and the patient was asked to look downward and outward.Then Ultipor nylon 6,6 Membrane was placed on the upper part of the bulbar conjunctiva for two seconds and the filter paper was peeled from the conjunctiva. Then the filter paper was placed over a glass slide and pressure was applied so that the impression from the filter paper got imprinted over the glass slide.

The imprinted glass slide was placed in the jar containing 95% ethanol for fixation followed by periodic acid schiff (PAS) stain and was counterstained with Mayer's haematoxylin and graded using Nelson's criteria.[3]

Statistical analysis was done by SPSS24, correlation was done using Chi square test and p value less than 0.05 was considered statistically significant.

Results

The mean age in this study population was 53 years. Total number of males involved were 111 and females were 89. The mean duration of type 2 diabetes mellitus in this study was 7.1 years. The duration of diabetes was classified as less than 10years and more than 10years,128 (64%) were less than 10 years and 72(36%) were more than 10years. Among these 116 (58%) were taking oral hypoglycaemic drugs and 83 (41.5%) were on both insulin and oral hypoglycaemic drugs. The Mean HbA1c level in this study was 8.3%. HbA1C was taken as the diagnostic tool for poor metabolic control in this study, which was graded according to American Diabetes Association (ADA) criteria.[4] Nearly 95 (47.5%) were in poor metabolic control group.

In Schirmer's test 1, 74 (37%) were normal whereas 56 (28%) had mild dry eye and 70(35%) had moderate dry eye. In Schirmer's test 2, 33(16.5%) were normal, 48 (24%) had mild dry eye, 103(51.5%) had moderate dry eye and 16(8%) with severe dry eye. Tear breakup time is one of the diagnostic tools for tear film instability, 29 (14.5%)had normal TBUT, 42(21%) had mild , 67 (33.5%) & 62 (31%) fall under moderate and severe dry eye categories respectively. Impression cytology was done for all the 200 diabetic patients, among them, 14 patients (7%) impression was inadequate. Of 186 with adequate impression, 83 (44.6%) had normal conjunctival morphology whereas 74(39.8%) and 29 (15.6%) had moderate & severe changes, respectively in conjunctival morphology (Figure 1) which was graded using Nelsons criteria. The final diagnosis of tear film instability was based on both Schirmer's test result and tear breakup time. It was found that 158 (79%) patients of type 2 Diabetes mellitus had tear film instability.

Tear film instability was found to be higher (91.7%) among >=60 years age group and increases with age. This was found in 85.4% of females and 73.9% of males. It shows that females with Diabetes mellitus were more prone to have tear film instability when compared to the males, which was statistically significant($p<0.01$). Changes in conjunctival morphology was found in 67.2% in>=60 years age group and nearly 45% in 45-59 years age group. It was confirmed that there is a statistically significant association between age and conjunctival morphology. Among them, 48.6% males and 64.2% of females had moderate to severe changes in the morphology of conjunctiva. This showed that, female patients were more prone to have conjunctival morphology changes when compared to the males with Diabetes mellitus. The first objective of this study was to associate the tear film instability with duration of type 2 Diabetes mellitus and poor metabolic control. In less than 10 years of duration, 96(75%) and in more than 10 years of duration, 62(86.1%) were found to have tear film instability which was not statistically significant. This proves that the tear film instability is not influenced by duration of type 2 Diabetes mellitus (Table 1).

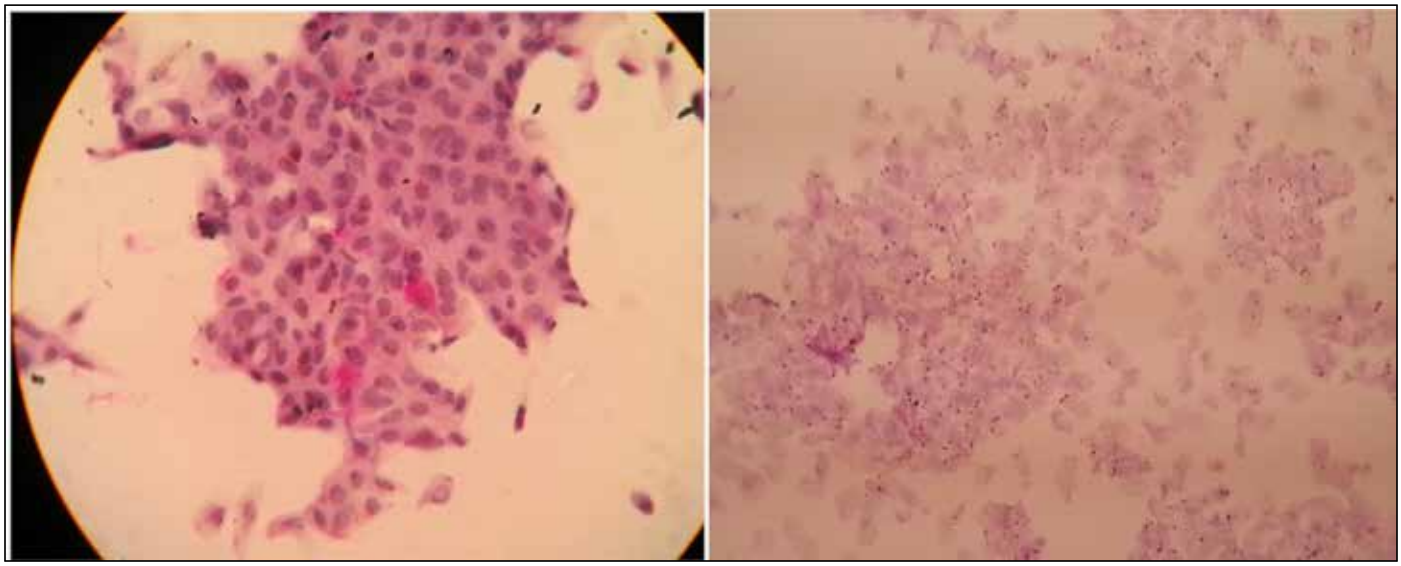

Figure 1: *conjunctival morphology*

Table 1: Duration of Diabetes Mellitus (years) vs Tear film status

Duration of DM (years)	Tear Film Status		Total
	Dry eye	Normal	
<10 years	9 6 (75.0%)	32(25.0%)	128
>= 10 years	6 2 (86.1%)	10 (13.9%)	72
Total	158	42	200

*Chi-square = 3.43; p value= 0.06; not statistically significant.

Table 2: HbA1C- control vs Tear film status

HbA1C- Control	Tear Film Status		Total
	Dry eye	Normal	
Normal/Good control(Upto 7%)	49(70.0%)	21(30.0%)	70
Fair Control (7.1-8%)	27(77.1%)	8(22.9%)	35
Poor Control (> 8%)	82(86.3%)	13(13.7%)	95
Total	158	42	200

*Chi-square statistic = 6.56; p value= 0.03; statistically significant.

Table 3: Duration of Diabetes Mellitus (in Years) Vs Impression Cytology of Conjunctiva

Duration of DM (years)	Impression Cytology of conjunctiva		Total
	Normal (Grade0-1)	ModerateSevere (Grade 2 or 3)	
10 years or less	65(55.6%)	52(44.4%)	117
> 10 years	18(26.1%)	51(73.9%)	69
Total	83	103	186

*Chi-square statistic =15.25; p value =<0.001, highly statistically significant.

Table 4 : HbA1c Vs Impression Cytology Of Conjunctiva

HbA1C- Control	Impression Cytology of conjunctiva		Total
	Normal (Grade 0-1)	Moderate/Severe (Grade 2 or 3)	
Normal/Good control (Upto 7%)	44(65.7%)	23(34.3%)	67
Fair Control (7.1-8%)	9(31%)	20(69%)	29
Poor Control (> 8%)	30(33.3%)	60(66.7%)	90
Total	83	103	186

*Chi-square statistic =18.82 ; p value= <0.001; statistically significant

The (Table 2) shows the association of tear film instability and HbA1C%. ADA criteria were implied to categorize the HbA1C level, out of 70 patients with good metabolic control, 49(70%) had tear film changes and out of 95 patients of poor metabolic control , 82(86.3%) had tear film instability. The proportion of study subjects with tear film instability was observed to be increasing with worsening of metabolic control. This was found to be statistically significant ($p<0.05$), implying that tear film instability is related to poor metabolic control rather than the duration of disease as discussed earlier.

The second objective, is to determine whether the changes in conjunctival morphology are related to the duration Diabetes mellitus or poor metabolic control. In less than 10 years of duration 52 patients (44.4%) and in more than 10 years of duration 51 (73.9%) were found to have moderate to severe changes in the conjunctival morphology which is highly statistically significant (p value = <0.001) (Table 3). This proves that the changes in the conjunctival morphology were influenced by duration of Diabetes mellitus.

(Table 4) shows the association between HbA1C and conjunctival cytology.out of 67 patients with good control 23(34.3%) had changes in CIC and out of 90 patients with poor metabolic control, 60 (66.7%) had changes in conjunctival cytology. This difference was statistically significant, and it clearly proves that changes in morphology of conjunctiva are related to poor metabolic control.

Discussion

In this study, out of 200 patients with type 2 diabetes mellitus 79% had tear film instability and 56% had changes in conjunctival morphology. Few studies have correlated dry eye and diabetes mellitus. Apart from cataract and retinopathy, recently ocular surface disorders, dry eye in particular have been reported among diabetes patients.[5] The mechanism of dry eye in type 2 diabetes mellitus is unclear, but autonomic neuropathy is found to be a cause. The possible reasons could be an exocrine dysfunction of the main lacrimal gland or development of unknown protiens like lactoferrin ,albumin, lipocalin, lysozyme in the tear fluids.[6] Damage to the microvasculature of the lacrimal gland can also lead to impaired function of the gland.

In a cohort study involving 3722 subjects, prevalence was 19.0% with subjects older than 80 years and 8.4% in subjects younger than 60 years. Age-adjusted prevalence was 16% in females compared to males 11.4%.[7,8,9]

Moss et al has proved that there is a higher incidence of dry eye among diabetic women. In this study, around 10% of females had tear film instability compared to males. In a study, by Masoud et al and Jin et al, it was found that the diabetic patients have less tear secretion and tear breakup time compared to the control.[10,11]

In another study, Seifart U et al found correlation between HbA1C and dry eye syndrome and they concluded that poor metabolic control has higher chance of dry eye(8). Even in this study, the correlation was found between HbA1C and tear film status along with and conjunctival cytology. 86.3% of patients, having poor metabolic control had tear film instability and 58.3 % had conjunctival morphology changes.

In a study by Nolan, he stated that the main disadvantages of impression cytology were some loss of morphological particulars and in cases of keratinizing lesions it was because of poor cell yield.[12] In another study, Chaparala P et al showed that lack of cells in the smears of conjunctival impression cytology may indicate hypovitaminosis A,

provided technical failure to access cellularity could be ruled out.[13] In our study, out of 200 patients, 186 patients' impression cytology was adequate for grading and 14 patients' impression was inadequate sample may be due to procedural and technical errors.

All the patients, who were diagnosed to have tear film instability and changes in the conjunctival morphology in this study, irrespective of their grading were prescribed artificial tear substitutes preferably preservative free, one drop three times a day for three months and were followed up. Patients, diagnosed to have moderate dry eye were asked to review every two months and for severe dry eye to review monthly.

Limitation

The current study elaborates the basic dry eye parameters namely Schirmer's and Tear breakup time and also the pathogenesis in the form of impression cytology. This study can further be improvised by including meibomian gland evaluation using Lipiscan or Lipiview.

Conclusion

Tear film instability was found to be more significantly associated in patients with poor metabolic control than with the duration of the type 2 Diabetes mellitus. Changes in conjunctival morphology was correlating significantly with both increase in duration and poor metabolic control. It should be made mandatory that dry eye be evaluated among all type 2 Diabetes mellitus patients and the treatment should be given accordingly, so that the complications can be prevented.

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