

Association of Dry Eye Disease and Diabetic Retinopathy with Glycated Hemoglobin at a Tertiary Care Unit of Karachi Pakistan

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ABSTRACT

OBJECTIVE: To investigate the association of dry eye disease and diabetic retinopathy (DR) with glycated haemoglobin at a tertiary care unit in Karachi, Pakistan.

METHODOLOGY: This cross-sectional observational study was conducted at Baqai Institute of Diabetology and Endocrinology, Baqai University Karachi, Pakistan, from July to December 2020. A total of 238 subjects having type 2, type 1, and gestational diabetes mellitus participated in this study. They went through a routine ophthalmic examination, breakup tear film time (BUT) test, Schirmer I test, staining fluorescein, and fundus photography performed to diagnose the DR. Baseline detail and biochemical parameters were recorded. Data analysis was done on statistical packages for the sciences social (SPSS) 20 version.

RESULTS: A total of 72 participants had dry eye disease (DED) conforming to a total prevalence of 30.25%; 11(4.6%) had severe dry eyes, 26(10.9%) had moderate dry eyes, 35(14.7%) had mild dry eyes whereas, 166(69.7%) participants had normal eyes. There was no significant association between gender, index mass body (BMI), smoking habits, history of family diabetes, and duration of Diabetes with DED. The frequency of retinopathy diabetic (DR) was registered as 23.5%; 29(24%) males and 27(23.1%) females, respectively.

CONCLUSION: Overall, a 30.3% frequency of dry eye in diabetic individuals was observed. It should improve by having consistent follow-ups after three to six months, providing a distinct difference in the condition compared to the non-affected individuals.

KEYWORDS: Dry eyes, ocular surface disease, Dryness in the eyes, deficiency tear, lacrimal function unit, Schirmer's test, Diabetes.

INTRODUCTION

Worldwide, Diabetes is a rising trend, and it is projected by the Diabetes International Federation (IDF) that around 537 million folks are surviving with Diabetes, with predictions expected to upsurge above 643 million individuals by 2030¹. In Pakistan, Diabetes is now known as a chronic disease due to adaptation of westernized diets and various changes in lifestyle and demographic features. According to the recent second National Pakistan Diabetes Survey (NDSP) 2016-2017, Diabetes has affected 26% of the country's population, which is alarming and a significant public health issue². Diabetes, if not have reasonable control, can cause chronic complications that include retinopathy, nephropathy, neuropathy, and heart and vascular diseases.³

Blindness's major cause is DR in developed and underdeveloped countries¹². The prevalence of diabetic retinopathy (DR) in Pakistan was 28.78%⁴. DR itself is a leading cause of blindness, and dry eye disease (DED) aggravates vision loss which usually may lead to poor quality of life⁵. DED has corneal complications such as superficial keratopathy punctuates, trophic ulceration, tear film hyperosmolarity, instability, neurosensory abnormalities, and persistent epithelial defects⁶. Hyperosmolarity and instability tear film are the procedures that cause dry eyes with Diabetes⁷. Tear film abnormality is a significant diabetic feature of the ocular disease surface due to low quality and tear functions that occur with the subnormal ocular surface⁸.

Dry eyes are commonly observed in the age group between 60-70 years⁹. It's because aging results in acinar degeneration and nuclear abnormalities that entirely change the Lacrimal unit's function. It has also been reported that male gender, prolonged Diabetes, and elevated glycated haemoglobin (HbA1c) levels were positively linked to greater severity of DR¹⁰. Direct relationship was also found in an investigation between HbA1c levels and the prevalence of DED. The greater the HbA1c levels, the more likely to acquire dry eye conditions⁶.

Early diagnosis of dry eyes has now become necessary for clinicians to determine the associated factors and to prevent visual acuity with early treatment. With the scarcity of data from this globe, we aim to assess the association of dry eye disease and diabetic retinopathy (DR) with glycated haemoglobin at a tertiary care unit in Karachi, Pakistan.

METHODOLOGY

This cross-sectional study was conducted at Baqai Institute of Diabetology and Endocrinology (BIDE), Medical Baqai University (BMU), Karachi – Pakistan. The study period was from July to December 2020; ethical approval was obtained from the Institutional Review Board (IRB) of BIDE. Each study subject was given a detailed methodology description, and written and verbal consent was obtained. Both males and females with known type 2 diabetes mellitus (DM), type I DM, and gestational DM, aged between 35-70 years, were included. Subjects with other types of DM and those taking other than Diabetes medications which can affect the production of tears were omitted from the study. Subjects with previous ocular surgery history, palsy Bell's person, Sjogren's syndrome, rheumatoid arthritis, or Parkinson's disease were also excluded.

Type II DM subjects were selected using a random sampling technique. Baseline details were obtained on a predesigned questionnaire. It includes diabetes duration, types of Diabetes, gender, age, smoking habit, alcohol habit, Diabetes family history, height, weight and blood pressure. Recent haemoglobin (Hb) A1c value and lipid profile levels were recorded from the hospital management system (HMS) of BIDE. A routine ophthalmic examination was done, which included a tear film breakup time (TBUT) test, Schirmer test, fluorescein staining and fundus photography for DR. Dry eyes were suspected based on a history of ocular discomforts such as soreness, gritty sensation, itchiness, redness, excessive watering of the eye, and blurred vision that improve after blinking. Subjects underwent lamp slit examination of surface ocular staining dye pattern with stain fluorescein. For the confirmation of the condition, a strip Schirmer test was made. The strip was placed at the middle junction, and the third lateral of the lower eyelid, and the amount of wetting was measured after 5 minutes. The condition was graded on the following scale: 0-5 mm; severe dry eye, 5-10 mm; moderately dry eye, 10-15 mm; mild dry eye, and ≥ 15 mm; normal tear function¹¹.

The glycemic index was targeted as HbA1c $< 7\%$ (good glycemic control) and $> 7\%$ (bad glycemic control)¹². Subject was considered dyslipidemic if having a serum total cholesterol > 200 mg/dl, serum LDL- cholesterol > 130 mg/dl, serum HDL- cholesterol < 40 mg/dl (for males) and < 50 mg/dl (for females), and serum triglycerides > 150 mg/dl¹³. Height was measured by directly measuring the length from the bottom of the feet to the highest point of the head. Weight was measured in kilograms by a weighing machine. BMI was calculated by dividing weight (kg)/height (m)². BMI < 23 kg/m² was considered normal, ≥ 23 -24.9 kg/m² overweight and ≥ 25 kg/m² obese per Asia Pacific Guideline¹⁴. Blood pressure was measured in a sitting position after 10 minutes of rest using a mercury sphygmomanometer. Hypertension was considered if the subject had blood pressure $\geq 140/90$ mmHg¹⁵.

Statistical analysis

Data was analyzed on Statistical Packages for Social Sciences (SPSS) version 20. Continuous variables were presented as mean \pm standard deviation (SD), while categorical variables were presented as numbers (percentages). The chi-square, ANOVA, and Kruskal-Wallis tests were applied where applicable to determine the association between variables.

RESULTS

A total of 238 individuals were assessed. **Table I** shows the mean age of subjects (121 males, 117 females) was 50.5 ± 11.85 years. The study subjects were primarily non-smokers, 169(81.3%), and married 214(90.7%). Cholesterol total, triglycerides, HDL, and LDL, were 161.28 ± 44.76 , 191.24 ± 126.53 , 32.75 ± 8.24 , and 112.15 ± 39.87 , respectively. Poor glycemic control was observed with mean HbA1c levels of 9.13 ± 1.99 . More than half of the subjects, 157(75.5%), had a family history of Diabetes, and 110 (46.2%) participants had Diabetes for less than five years.

Table II represents the assessment of tear meniscus height using Schirmer's strip. Out of 238 subjects, 11(4.6%) had severe dry eyes, 26(10.9%) had moderate dry eyes, 35(14.7%) had mild dry eyes whereas, 166(69.7%) individuals had normal eyes. The overall frequency of dry eye in diabetic individuals was found to be 72(30.25%).

In males, the association was found to be 63.6% for severe, 53.8% for moderate, and 40% for mild dry eyes, whereas, in females, the association was 36.4%, 46.2%, and 60%, respectively. All the individuals lie in the obese range of $\geq 25 \text{ kg/m}^2$ for normal to severe dry eyes. Individuals with a positive history of Diabetes and a duration of fewer than five years suffered from moderate to severe dry eyes. There was no significant association between gender, body mass index (BMI), smoking habits, family history of Diabetes, and duration of Diabetes with tear breakup time (TBUT), p -value < 0.05 . Upon evaluating the relationship between biochemical parameters with TBUT, poor glycemic control was observed in severe (8.87 ± 1.04), mild (9.45 ± 2.31), and moderate dry eyes (9.84 ± 1.33). No significant association was found between lipid profile, HbA1c, and TUBT, while a significant association was found in cholesterol levels among severe (170 ± 53.39), mild (186.86 ± 59.23), moderate (173.94 ± 46.93), and normal eyes (152.83 ± 38.58) p -value = 0.03 (**Table III**).

In participants who have Diabetes, the prevalence of diabetic retinopathy was found to be 23.5%. Among 56(23.5%) individuals having retinopathy, 29(24%) were males, whereas 27(23.1%) were females (**Table IV**). Furthermore, **Table IV and Table V** show the association of diabetic retinopathy with dry eye disease and gender. In contrast, no association significantly was found between diabetic retinopathy, dry eye disease, and gender was found.

Table I: Baseline characteristics of studied subjects

Variables		N (%) or Mean ± S.D
N		238
Gender	Male	121(50.8%)
	Female	117(49.2%)
Age (years)		50.52±11.85
Marital status	Single	13(5.5%)
	Married	214(90.7%)
	Widow	9(3.8%)
Body mass index (kg/m²)		28.94±5.28
Systolic blood pressure (mm Hg)		124.15±18.51
Diastolic blood pressure (mmHg)		77.43±9.41
Type of Diabetes	Type 1	3(1.3%)
	Type 2	234(98.3%)
	Gestational	1(0.4%)
Smoking habit	No	169(81.3%)
	Ex-smoker	19(9.1%)
	Current smoker	20(9.6%)
Alcohol addiction	No	206(99%)
	Yes	2(1%)
Family history of Diabetes	No	51(24.5%)
	Yes	157(75.5%)
HbA1c (%)		9.13±1.99
Cholesterol (mg/dl)		161.28±44.76
Triglyceride(mg/dl)		191.24±126.53
High density lipoprotein(mg/dl)		32.75±8.24
Low-density lipoprotein (mg/dl)		112.15±39.87
Duration of DM	≤5 years	110(46.2%)
	5 to 10 years	57(23.9%)
	>10 years	71(29.8%)

Table II: Assessment of tear meniscus height using Schirmer's strip method

Schirmer's strip test (mm)	n (%)	Overall
N	238	72(30.25%)
≤5	11(4.6%)	
6-10	26(10.9%)	
11-15	35(14.7%)	
>15	166(69.7%)	

Table III: Association of tear film breakup time (TBUT) with baseline and biochemical parameters

Variable		TBUT (mm)				P-value
		≤5	6-10	11-15	>15	
N		11	26	35	166	
Age (years)		47.91±12.58	48.54±11.75	51.43±11.24	50.81±11.99	0.868
Gender	Male	7(63.6%)	14(53.8%)	14(40%)	86(51.8%)	0.471
	Female	4(36.4%)	12(46.2%)	21(60%)	80(48.2%)	
Systolic blood pressure (mm Hg)		137.14±33.02	123.78±19.16	124.34±15.95	123.54±18.03	0.77
Diastolic blood pressure (mmHg)		77.14±11.13	78.87±9.16	77.16±8.8	77.28±9.57	0.895
Body mass index (kg/m ²)		30.05±3.95	29.42±4.79	28.2±4.19	28.97±5.65	0.772
Family history of Diabetes	No	2(28.6%)	5(21.7%)	10(31.2%)	34(23.3%)	0.786
	Yes	5(71.4%)	18(78.3%)	22(68.8%)	112(76.7%)	
Duration of Diabetes	≤5 years	6(54.5%)	12(46.2%)	9(25.7%)	83(50%)	0.114
	5-10 years	3(27.3%)	9(34.6%)	11(31.4%)	34(20.5%)	
	>10 years	2(18.2%)	5(19.2%)	15(42.9%)	49(29.5%)	
Type of Diabetes	Type 2	11(100%)	26(100%)	35(100%)	162(97.6%)	0.623
	Other	0(0%)	0(0%)	0(0%)	4(2.4%)	
HbA1c (%)		8.87±1.04	9.45±2.31	9.84±1.33	8.93±2.06	0.275
Cholesterol (mg/dl)		170±53.39	186.86±59.23	173.94±46.93	152.83±38.58	0.032
Triglyceride(mg/dl)		250.5±238.45	176.07±64.43	211.94±128.6	186.01±128.9	0.717
High-density lipoprotein (mg/dl)		31.75±6.13	35.14±7.44	36.18±7.54	31.53±8.45	0.122
Low-density lipoprotein (mg/dl)		98.25±40.94	123.67±53.73	121.05±35.46	108.64±38.08	0.432

Data presented as mean ± SD or n (%); P-value<0.05 considered statistically significant.

Table IV: Association of Retinopathy with TBUT

Retinopathy	TBUT (mm)				P-value
	≤5	6-10	11-15	>15	
NO#	11	26	35	166	
No	9(81.8%)	21(80.8%)	26(74.3%)	126(75.9%)	0.905
Yes	2(18.2%)	5(19.2%)	9(25.7%)	40(24.1%)	

Data presented as n (%); P-value<0.05 considered as statistically significant; NO# = numbers

Table V: Association of retinopathy with gender

Retinopathy	Male	Female	P-value	Overall
N	121	117	-	238
No	92(76%)	90(76.9%)	0.871	182(76.5%)
Yes	29(24%)	27(23.1%)		56(23.5%)

Data presented as n (%); P-value<0.05 considered as statistically significant

DISCUSSION

Overall, a 30.3% frequency of dry eye in diabetic individuals was observed, among which 4.6% had severe dry eyes, 10.9% had moderate dry eyes, and 14.7% had mild dry eyes. The prevalence of diabetic retinopathy was 23.5%, and participants were observed with poor glycemic control and bad triglyceride levels. The DED in diabetic patients varies in different populations. Fuerst N et al.¹⁶ found a 47.8% dry eye prevalence higher than our study.

Dry eyes were more frequent in females than males, in line with a recent study that showed females were more prone to dry eye disease than males¹⁷. Females were more inclined to males, which may be due to the onset of menopause that causes decreased estrogen levels in females and leads to reduced tear film⁹. Misra SL et al.¹⁸ reported that due to the lesser production of androgens, a type of protective hormone, there is an upsurge in the incidence of dry eye disease in women. However, other studies have negated the association of gender in diabetic individuals with dry eye disease¹⁹. This research revealed that reduced tear formation in some diabetic individuals is linked to autonomic nervous system dysfunction²⁰. We found the component of total cholesterol were similar in levels among diabetic participants with DED and non-DED. Our data show no association between dry eye disease and lipid profile. In our study, the prevalence of diabetic retinopathy was 23%, and gender had no statistically significant influence on the condition. We observed most participants with less than five years of Diabetes, in contrast with ul Islam Q 2017²¹ studies who found participants with longer diabetes duration.

In this investigation, we observed participants with poor glycemic control; however, the association of HbA1c with the dry eye was statistically insignificant, in contrast with the findings of other studies²²⁻²⁶, which found a strong positive connection between HbA1c and dry eye. Manjula TR 2019²⁷ stated that DM management with dry eyes is statistically significant. A study from the Asian population also found a strong association between dry eyes with poor glycemic control²⁸.

CONCLUSION

Overall, a 30.3% frequency of dry eye in diabetic individuals was observed, among which 4.6% had severe dry eyes, 10.9% had moderate dry eyes, and 14.7% had mild dry eyes. It may improve by having consistent follow-ups after three to six months, providing a distinct difference in the condition compared to the non-affected individuals.

Limitations

This study has some limitations due to its relatively small sample size and the fact that it was conducted at only one clinical site. Moreover, menopausal history, which significantly affects the development of DED, was lacking in our study.

Ethical Permission: Baqai Medical University, Karachi, IRB letter No. BIDE/IRB/SSULTAN/08/20/0234.

Conflict of Interest: No conflicts of interest.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTIONS

Sultan S:	Concept, design, edited and approved the manuscript
Khazada MA:	Interpretation of data, edited and approved the manuscript
Shakeel A:	Interpretation of data, edited and approved the manuscript
Ahmed N:	Literature search, interpretation of data, and wrote the manuscript
Fawwad A:	Concept, design, Edit and approved the final manuscript
Basit A:	Concept, design, Edit and approved the final manuscript

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