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Dry eye syndrome in diabetic children

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PURPOSE. *To compare the symptoms, signs, and results of objective tests for dry eye syndrome (DES) in type 1 diabetes mellitus (T1DM) patients and controls.*
METHODS. *A total of 104 children with T1DM and 104 age- and sex-matched controls were compared in terms of the symptoms, signs, and results of objective tests for DES. Duration of T1DM, presence of diabetic retinopathy, mean hemoglobin A1c level, pubertal status, and a history of accompanying autoimmune disease were noted in T1DM group. Analysis of variance, multivariate regression analysis, Student t, Mann-Whitney U, and chi-square tests were used for statistical analysis.*
RESULTS. *A total of 15.4% of diabetic children complained of dry eye symptoms, versus 1.9% of the controls (p=0.029). Dry eye signs were detected in 7.7% of diabetic children, versus 0.96% of controls (p=0.034). Tear break-up time (TBUT) and Schirmer test results were significantly lower in T1DM group than controls (p=0.018, p=0.024, respectively). A total of 7.7% of diabetic children had definite and 0.96% had probable diagnosis of DES, versus none of the controls (p=0.03). TBUT and Schirmer test results were significantly lower in patients with more than 10 years duration of T1DM (p<0.001 for both).*
CONCLUSIONS. *The prevalence of symptoms, signs, and definite diagnosis of DES are higher and basal tear secretion and tear film stability are lower in diabetic children than controls. Duration of T1DM is the only disease-related variable which is associated with basal tear secretion and tear film stability. (Eur J Ophthalmol 2007; 17: 873-8)*

KEY WORDS. *Diabetes mellitus, Dry eye syndrome, Schirmer test, Tear film break-up time*

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INTRODUCTION

Dry eye syndrome (DES) refers to disorders of the tear film caused by reduced tear production, poor tear quality, or excessive tear evaporation. These disorders are associated with signs and symptoms of ocular discomfort such as foreign body sensation, burning, itching, photophobia, conjunctival discharge, filaments, conjunctival luster, erythema, and dryness of bulbar conjunctiva and may cause disease of the ocular surface (1).
As a systemic disease, diabetes mellitus (DM) has several well known ocular complications such as diabetic retinopathy, neovascular glaucoma, cataract, refractory deviations, ptosis, oculomotor nerve palsy, and hordeolosis (2). In patients with long-lasting diabetes, damage to the microvasculature of the lacrimal gland together with autonomic neuropathy might impair lacrimation. Diabetic sensory neuropathy of the cornea can also play a role in decreased tear secretion.
Several previous studies have investigated the relationship between DM and DES. Although some found an increased risk for DES among diabetic individuals (3-6),

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others found neither a significant decrease in the amount of aqueous tear flow nor impaired tear break up time (TBUT) among insulin-dependent diabetic patients (7). Moreover, the relation between the disease-related variables, such as the duration of disease, glycemic control, and pubertal status, which are known to be associated with other diabetic complications, and DES is not certain.

In this study, we aimed to compare the symptoms, signs, and results of objective clinical tests for DES in patients with Type 1 diabetes mellitus (T1DM) and age- and sex-matched controls.

MATERIALS AND METHODS

A total of 107 children with T1DM attending the pediatric endocrinology department of Diskapi Children's Hospital and 104 age- and sex-matched controls were examined. Controls were derived among the healthy school children. Exclusion criteria for both groups consisted of smoking; receiving glucocorticoids, antihistamines, birth control pills, or diuretics, as these drugs are known to affect tear secretion (8); usage of ocular topical treatment within last 6 months; previous ocular laser or surgical treatment; presence of any ocular disease other than dry eye disease and diabetic retinopathy; and presence of any systemic disease other than DM and accompanying autoimmune diseases (AAD). Three patients were excluded from the study group due to usage of ocular topical treatment within the last 6 months.

The following symptoms were queried and recorded: foreign body sensation, burning, itching, and photophobia. Signs of ocular involvement such as conjunctival discharge, filaments, conjunctival luster, erythema, and dryness of bulbar conjunctiva were determined by slit lamp examination. These variables were evaluated on a scale of 0 to 4 where 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.

The following objective tests were carried out in the following sequence: Schirmer test with application of topical anesthesia, fluorescein staining, tear film break-up time (TBUT), and rose Bengal (RB) dye test.

Fluorescein staining was done by touching the inferior fornix with a dry fluorescein strip while the patient looked forward. Any staining on the cornea was recorded and graded on a scale of 0 to 3 where 0=no staining of corneal epithelial surface, 1=mild staining limited to <1/3 of cornea, 2=moderate staining occupying <1/2 of cornea, 3=severe staining of >1/2 of cornea. RB staining was performed by instilling a drop of 1% RB dye into the inferior fornix of each eye and any staining of conjunctiva or cornea was recorded under a slit lamp. The degree of staining was recorded for temporal conjunctiva, cornea, and nasal conjunctiva on a scale of 0–3 each. These three scores were added to obtain total scores of 0–9 for each eye. In the evaluation process the staining induced by the Schirmer strip was disregarded.

Cutoff values of the tests were as follows: Schirmer test ≤5 mm/5 min, TBUT ≤10 s, RB score >3, and fluorescein staining ≥1 (6). Children were diagnosed with definite DES if two or more tests were abnormal and probable DES if only one test was abnormal. The diagnosis of DES in this study was made by extrapolating the Japanese (9) and Copenhagen criteria (10).

For the study group; duration of T1DM, presence of diabetic retinopathy (determined by dilated funduscopy), mean hemoglobin A1c (HbA_{1c}) level, pubertal status, and a history of AAD were noted. Pubertal status was evaluated by Tanner standards. Children were divided into two groups according to their pubertal stages; ones at P1 stage were regarded as prepubertal while ones at P2-5 as pubertal. According to duration of T1DM, children were divided into three groups (Group A: <5 years, Group B: 5–10 years, Group C: >10 years). According to mean HBA1c level, children were divided into three groups (Group A: <7%=good control, Group B: 7–9%=moderate control, Group C: >9%=poor control).

Scores of symptoms and clinical signs and the results of objective tests for DES were compared between the two groups. Relation between the results of objective tests of DES (TBUT and Schirmer test) and T1DM related variables were investigated in the study group. All the investigations were performed according to the guidelines of Declaration of Helsinki. Informed consent was taken from a parent of each participant.

Chi-square test was used to compare the categorical variables. Mann-Whitney U and Student t-tests and analysis of variance (ANOVA) were used to compare the continuous variables. $p<0.05$ Was regarded as statistically significant. For further analysis within the study group, a multivariate regression analysis was performed to evaluate the independent contribution of age, sex, and duration of T1DM on TBUT and Schirmer test results. SPSS 13.0 statistical program was used for the analysis (SPSS, Inc.).

RESULTS

There were 57 male and 47 female subjects in both groups. The mean±standard deviation (SD) age was 12.3±5.8 years (range 7.0 to 17.6 years) in T1DM group, 12.7± 5.6 years (range 7.4 to 17.4 years) in the control group. There was no significant difference in age between the two groups (Student t-test, p=0.98).

Among 104 children with T1DM, 17 (16.3%) had a history of accompanying autoimmune disease (16 had Hashimoto thyroiditis and 1 had celiac disease). Thirty-four were prepubertal while 70 were pubertal. The mean±SD of duration of T1DM was 6.1±3.4 years (range 1 month to 13.2 years). The mean±SD of mean HBA1c level was 8.4±3.4% (range 6.6% to 17.7%). Diabetic retinopathy was not detected in any diabetic child.

Symptoms and clinical signs of DES are outlined in Table I. The scores of dry eye symptoms (foreign body sensation, burning, itching, and photophobia) were significantly higher in T1DM group (Student t-test, p=0.028, p=0.032, p=0.018, p=0.033, respectively). Sixteen children (15.4%) in T1DM group and 2 children (1.9%) in the control group complained of dry eye symptoms; therefore, the prevalence of dry eye symptoms was also significantly higher in the T1DM group (χ^2=8.8, p=0.029). As the scores of dry eye signs (conjunctival discharge, filaments, conjunctival luster, erythema, and dryness of bulbar conjunctiva) were concerned, there were no significant differences between T1DM and the control group (Student t-test, p>0.05 for all comparisons). Dry eye signs were detected in 8 children (7.7%) in the T1DM group versus in 1 child (0.96%) in the control group; therefore, the prevalence of dry eye signs was significantly higher in T1DM group (χ^2=4.9, p=0.034).

The results of objective tests for DES are outlined in Table II. As the results of TBUT and Schirmer test were concerned, there were statistically significant differences between T1DM and the control group (Student t-test, p=0.018 and p=0.024, respectively). However, there were no statistically significant differences between the two groups in terms of RB and fluorescein staining scores (Student t-test, p=0.59 and p=0.62, respectively).

Data about the relation between the results of objective tests of DES (TBUT and Schirmer test) and T1DM related variables are outlined in Table III. Among 104 children with T1DM, 34 were prepubertal and 70 were pubertal. There were no significant differences in TBUT and Schirmer test results between children with or without puberty (Student t-test p=0.78, p=0.81, respectively). According to HBA1c mean level children were divided into three groups (Group A:<7%=good control, Group B: 7–9%=moderate control,

TABLE I - SCORES OF SYMPTOMS AND CLINICAL SIGNS OF DRY EYE SYNDROME (DES), MEAN (range)

Symptoms and signs of DES	Group	Result	p value
FBS	DM	1.7 (0–4)	0.028
	Control	0.4 (0–2)	
Burning	DM	1.5 (0–4)	0.032
	Control	0.4 (0–2)	
Itching	DM	1.9 (0–4)	0.018
	Control	0.3 (0–2)	
Photophobia	DM	1.3 (0–3)	0.033
	Control	0.2 (0–1)	
Conjunctival erythema	DM	0.6 (0–4)	0.52
	Control	0.2 (0–1)	
Conjunctival discharge	DM	0.5 (0–4)	0.58
	Control	0.1 (0–1)	
Conjunctival luster	DM	1.0 (0–3)	0.53
	Control	0.4 (0–1)	
Filaments	DM	0.1 (0–2)	0.71
	Control	0.0 (0–0)	
Dryness of bulbar conjunctiva	DM	0.4 (0–3)	0.51
	Control	0.1 (0–1)	

These variables were evaluated on a scale of 0–4 where 0=none, 1=Mild, 2=Moderate, 3=Severe, and 4= Very severe.
FBS = Foreign body sensation; DM = Diabetes mellitus

Group C: >9%=bad control). There were 26, 45, and 33 children in Groups A, B, and C, respectively. ANOVA revealed that there were no significant differences among these subgroups in TBUT and Schirmer test results [F(2,101)=0.32, p=0.88, F(2.101)=0.41, p=0.84 respectively]. Among 107 children with T1DM, 17 (16.3%) had a history of AAD. There were no significant differences in TBUT and Schirmer test results between children with or without a history of AAD (Mann-Whitney U test p=0.59, p=0.62, respectively). According to the duration of T1DM, children were divided into three groups (Group A: <5 years, Group B: 5–10 years, Group C: >10 years). There were 40, 43, and 21 children in Groups A, B, and C, respectively. ANOVA revealed that TBUT and Schirmer test results were significantly different among these subgroups [F(2,101)=146.3, p<0.001, F(2.101)=152.1, p<0.001, respectively]. Post hoc Tukey analysis showed that while there were no differences between Group A and Group B, TBUT and Schirmer test results were significantly lower in Group C (p<0.001 for both comparisons). Multivariate re-

TABLE II - OUTCOMES OF OBJECTIVE TESTS OF DRY EYE SYNDROME (DES) - MEAN ± STANDARD DEVIATION (range)

Objective tests of DES	Group	Result	p value
RB dye test	DM	0.3 (0–5)	0.59
	Control	0.1 (0–1)	
TBUT (seconds)	DM	11.1±2.6 (5–15)	0.018
	Control	16.8±2.8 (11–19)	
Schirmer test (mm/5 min)	DM	8.2±3.6 (3–11)	0.024
	Control	12.7±4.2 (9–18)	
Fluorescein staining	DM	0.1 (0–3)	0.62
	Control	0.0 (0–0)	

RB = Rose Bengal; DM = Diabetes mellitus; TBUT = Tear film break-up time

TABLE III - RELATION BETWEEN THE RESULTS OF OBJECTIVE TESTS OF DRY EYE SYNDROME (DES) (TBUT and SCHIRMER TEST) AND DIABETES MELLITUS (DM)-RELATED VARIABLES - MEAN ± STANDARD DEVIATION (range)

DM-related variables	TBUT (seconds)	Schirmer test (mm/5 min)	p value
Puberty			
+ (n=70)	10.7±2.8 (6–15)	8.0±3.3 (3–11)	0.78, 0.81
– (n=34)	11.4±2.2 (5–14)	8.4±3.1 (4–10)	
HbA1c mean level			
≤7% (n=26)	11.4±2.9 (7–15)	8.0±3.8 (4–11)	0.88, 0.84
7–9% (n=45)	11.2±3.1 (6–14)	8.2±3.2 (4–10)	
≥9% (n=33)	10.7±3.4 (5–15)	8.3±3.2 (3–10)	
AAD			
+ (n=17)	9.4±2.1 (5–11)	7.4±3.1 (3–8)	0.59, 0.62
– (n=77)	11.9±2.7 (6–15)	9.7±3.6 (5–11)	
Duration of DM, yr			
≤5 (n=40)	13.1±2.2 (8–15)	9.9±3.0 (6–11)	<0.001, <0.001
6–9 (n=43)	11.5±2.1 (6–12)	8.4±2.9 (4–10)	
≥10 (n=21)	9.8±2.0 (5–11)	6.7±2.1 (3–8)	

TBUT = Tear film break-up time; AAD = Accompanying autoimmune disease

gression analysis revealed a significant effect of duration of T1DM on TBUT and Schirmer test results (t=3.29, p<0.001, t=3.67, p<0.001, respectively), in addition to effect of age (t=1.63, p<0.05; t=1.87, p<0.05, respectively) and sex (t=1.78, p<0.05; t=1.94, p<0.05, respectively).

In T1DM group, Schirmer test, TBUT, and RB staining results were abnormal in 6 children for each and fluorescein staining was abnormal in 9 children. Results of these tests were normal in all children in the control group. Therefore, 8 children (7.7%) had definite and 1 child (0.96%) had probable diagnosis of DES in T1DM group, versus no children in the control group. The prevalence of DES was significantly higher in diabetic children (χ^2=5.2, p=0.03). Data about the patients with diagnosis of DES are outlined in Table IV.

DISCUSSION

Dry eye can result from either interruption of the tearing reflex pathways or from any process that affects the ability of the lacrimal gland to secrete (11). In diabetes, it is possible that damage to the microvasculature of the lacrimal gland together with autonomic neuropathy may contribute to impaired function of the gland (11). Sensory neuropathy of the cornea may also play a role (11).

Moss et al examined risk factors for the prevalence of DES in a population-based cohort. The cohort was aged between 48 and 91 years. They reported that age and sex were independently associated with DES. After controlling for age and sex, the following factors were also reported as independently and significantly associated with dry eye: history of arthritis, smoking status, caffeine use, history of thyroid disease, history of gout, total to high-density lipoprotein cholesterol ratio, diabetes, and multivitamin use (3).

Moss et al examined the 5-year incidence of DES and associated risk factors in a population-based study. The population was aged between 43 and 84 years. They reported that the incidence of dry eye was significantly associated with age (p<0.001) and after adjusting for age, incidence was greater in subjects with a history of allergy or diabetes, who used antihistamines or diuretics, and with poorer self-rated health (4).

In a case-control retrospective study, Seifart et al compared 92 patients with diabetes types I and II and aged from 7 to 69 years with a group of normal healthy controls and demonstrated that KCS was more common in diabetic patients (5). In their study, 52.8% of all diabetic subjects complained of dry eye symptoms, versus 9.3% of the controls. An abnormal TBUT value was found in 94.2% of the diabetics and in only 5.8% of the controls. An abnormal Schirmer test result was observed in 26% of the diabetics and in 16% of the normal controls. Pathologic conjunctival epithelium (grade III–V after Tseng) was found in 86% of the diabetic patients and in 6.7% of the healthy subjects. Among the type II diabetic patients, 70% had proven DES, while 57% with type I diabetes had this. A correlation was found between the HBA1c values and the presence of DES. They concluded that the higher the HBA1c values, the higher the rate of DES.

Kaiserman et al compared the prevalence of KCS in a

TABLE IV - DIABETIC PATIENTS WITH DIAGNOSIS OF DRY EYE SYNDROME (DES)

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Diagnosis of DES	D	D	D	D	D	D	D	D	P
Schirmer test (mm/5 min)	6.3, 6.9	5.8, 5.2	3.2, 3.6	4.5, 4.8	3.8, 4.1	4.7, 4.1	3.0, 3.3	3.5, 3.1	6.2, 7.1
TBUT (seconds)	8, 5	11, 12	6, 5	7, 5	8, 6	11, 11	6, 5	5, 7	12, 14
RBSS	5, 6	4, 3	6, 5	6, 6	2, 2	2, 1	5, 5	4.4	1, 1
FSS	2, 2	3, 2	3, 2	2, 3	3, 4	3, 3	1, 1	3, 2	2, 2
Sex	F	F	F	F	M	M	M	M	M
Puberty	+	+	+	+	+	+	+	+	–
HBA1c mean level	8.2%	6.9%	11.2%	9.4%	10.5%	6.8%	7.3%	9.3%	11.2%
Duration of DM (years)	11.4	8.9	13.1	9.2	10.1	7.4	12.8	10.2	6.2
AAD	HT	—	HT	—	—	—	—	—	—

D = Definite; P = Probable; TBUT = Tear film break-up time; RBSS = Rose Bengal staining score; FSS = Fluorescein staining score; HBA1c = Hemoglobin A1c; DM = Diabetes mellitus; AAD = Accompanying autoimmune disease; HT = Hashimoto thyroiditis

prospective cohort of 22,382 diabetic patients with that in the general population. All patients (159,634) were older than 50 years; of those, 22,382 (14.0%) had diabetes. They reported that KCS was significantly more common among diabetic patients and poor glycemic control (mean HbA1c levels) correlated with increased artificial tear use in diabetic patients (6).

Goebbels et al compared 86 Type 1 diabetics (>30 years duration of DM) with retinopathy and 84 nondiabetic controls (age- and sex-matched) by fluorophotometry of tear secretion, Schirmer test, impression cytology of the conjunctival epithelium, and TBUT. They reported that diabetics showed decreased Schirmer test readings (without topical anesthesia) and significantly more frequent and pronounced signs of conjunctival metaplasia. They concluded that reflex tearing and conjunctival epithelium were the only affected variables of KCS among Type 1 diabetics with more than 30 years duration of disease (7).

In this study, we evaluated Type 1 diabetic children and age- and sex-matched controls. We found that the prevalence of symptoms, signs, and definite diagnosis of DES were significantly higher in diabetic children than controls. In addition, diabetic children without the symptoms, signs, and definite diagnosis of DES still had lower TBUT and Schirmer test results than controls. The only disease-related variable which was found to be associated with DES was duration of disease. Therefore, we advise screening for DES among Type 1 diabetic patients with more than 10 years duration of disease.

Proprietary interest: None.

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