Original Article

Ocular manifestations of Type 1 diabetes mellitus in pediatric population

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Context: To evaluate the necessity of ocular screening in Type 1 diabetes mellitus (DM). **Aims:** This study aims to investigate the diabetes-related ocular changes according to the glycosylated hemoglobin (HbA1c) level and duration of diabetes in children and compare the results with nondiabetic healthy children. **Settings and Design:** Observational cross-sectional study designed by ophthalmology and pediatric endocrinology clinics. **Subjects and Methods:** Forty-two children with Type 1 DM, 42 healthy gender- and age-matched children as controls were enrolled. All patients underwent ophthalmic and physical examination, with a review of medical history and current medication. HbA1c level, best corrected visual acuity, intraocular pressure (IOP), central corneal thickness (CCT), tear break-up time (BUT), Schirmer test, dilated fundus examination findings, central retinal thickness (CRT), and total macular volume (TMV) measurements were noted. **Statistical Analysis:** Descriptive statistics, Student's *t*-test, Mann–Whitney U-test, Chi-square test for comparison of the group parameters and correlation analyses (Spearman analysis) were performed with SPSS statistical software 17.0 (SPSS Inc., Chicago, IL, USA). **Results:** Type 1 DM group exhibited significantly reduced Schirmer test, increased IOP and decreased retinal thickness relative to the age-matched control group ($P < 0.05$) but no statistically significant difference was found for the BUT ($P = 0.182$) and for the CCT ($P = 0.495$). The correlations between the age, duration, HbA1c and IOP, BUT, Schirmer test, TMV, CRT measurements did not reach statistical significance. **Conclusions:** More frequent screening may be needed for complications, including neuropathy-related dry eye syndrome, IOP changes, and diabetic retinopathy in children with Type 1 DM.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.194336

Quick Response Code:

Key words: Corneal thickness, diabetic retinopathy, dry eye syndrome, Type 1 diabetes mellitus

Diabetes mellitus (DM) as a systemic disease, has several well-known microvascular complications such as diabetic retinopathy (DR), neuropathy, and nephropathy.[1] Diabetes-related autonomic neuropathy can involve ocular structures including lacrimal gland, cornea, and retina. The prevalence of DR in young children is low (varies from 10% to 35%), depending on the different studies[2,3] but the risk of developing microvascular complications may increase during the teenage years.[4,5] The detection of these microvascular complications needs careful examination of an anterior and posterior segment of the eye through a purposeful screening program.

In patients with diabetes, lacrimation might be impaired by autonomic neuropathy and damage to the microvasculature of the lacrimal gland.[6] Furthermore, there are studies suggesting that Type 2 DM is commonly associated with thicker corneas[7,8] and increased intraocular pressure (IOP).[9,10] There is evidence suggesting that neuronal changes have an important role in the development of DR in patients with Type 2 DM.[11] Additionally in a recent study, the retinal thickness was found to be decreased in subjects with Type 1 DM and minimal DR compared with nondiabetic controls.[12] Hence, diabetes-related neuronal changes may have an important role in the development of DR, dry eye syndrome (DES), and glaucoma that may cause clinical or subclinical microvascular changes.

The aim of this study was to evaluate the diabetes-related ocular changes in a group of diabetic children and to compare the results with healthy children. Therefore, this study was undertaken to ascertain whether children with diabetes have impairment due to microvascular changes.

Subjects and Methods

The prospective cross-sectional study included 45 patients with Type 1 DM at a pediatric clinic of a state hospital in a consecutive manner. The patients were consulted to Ophthalmology Department with the diabetic eye disease screening program, and three children were issued because of low cooperation during the examination. Hence, 42 children with clinically diagnosed Type 1 DM, 42 healthy gender- and age-matched children as controls were enrolled in this study. Inclusion criteria were no previous known macular or other retinal changes, best-corrected Early Treatment DR Study (ETDRS) visual acuity of >1.0, refractive error within ± 6 diopters (D), and no ophthalmic or systemic disease other

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Manuscript received: 12.12.15; Revision accepted: 27.07.16

Cite this article as: Akil H, Buluş AD, Andiran N, Alp MN. Ocular manifestations of Type 1 diabetes mellitus in pediatric population. Indian J Ophthalmol 2016;64:654-8.

than Type 1 DM. Subjects were excluded if they had an eye condition that might interfere with the study results, such as a history of ocular surgery, laser treatment, chronic or recurrent inflammatory eye diseases, intraocular trauma, current use of any ophthalmic or systemic steroid.

To compare the metabolic status of diabetic and nondiabetic subjects, venous blood samples were taken to determine glycosylated hemoglobin (HbA1c) levels. It defines the average blood glucose level of the previous 2–3 months and reflects the success of diabetes therapy. Usually, 4–6.4% of HbA1c. Higher values are a sign of insufficient blood glucose control.

All patients underwent ophthalmic and physical examination, with a review of medical history and current medication. Age, gender, onset of DM, and HbA1c level were recorded. Visual acuity was measured using an ETDRS chart at 4 meters. IOP was measured by noncontact tonometer (Topcon CT-80A, Japan). All patients had a dilated binocular indirect ophthalmoscopy using a +90 D condensing lens and slit-lamp biomicroscopy.

DR was defined as the presence of leaking blood vessels, retinal swelling, such as macular edema, pale, fatty deposits on the retina (exudates), damaged nerve tissue (cotton-wool spots), and any changes in the blood vessels (neovascularization).

Dry eye was confirmed by means of a set of tests performed in a successive manner: Tear film break-up time (BUT) and the Schirmer test. The conjunctiva and cornea were examined using a slit-lamp. BUT was assessed by measuring the time interval between a complete blinking and the formation of dry spots in a fluorescein stained tear film and that of 10 seconds (s) or less was considered abnormal.

The Schirmer test is the most used and easily performed test for the evaluation of DES. The Schirmer I test (without anesthesia) measures both basal and reflex tearing, and the Schirmer II test (with anesthesia) measures only the basal secretion of tearing with topical anesthesia instilled. Schirmer with anesthesia test for basal secretion was applied with a filter strip (SNO* Strips, Lab Chauvin, Aubenas, France) located inferior-temporally without touching the cornea and considered abnormal if wetting of the strip was 5 mm or less in 5 min.

Central corneal thickness (CCT) was measured by ultrasound pachymeter (IOPac Advanced, Heidelberg Engineering GmbH, Germany).

The central macular thickness was measured with optical coherence tomography (OCT) using the Stratus OCT™ (software version 4.0.1, Model 3000, Carl Zeiss Meditec, Dublin, CA, USA) with a dilated pupil. Six radial OCT scans were obtained in the center of the macula. For analysis of the retinal thickness, the macula was divided into three areas: The fovea with a diameter of 1 mm, the pericentral area (doughnut-shaped ring with an inner diameter of 1 mm and an outer of 3 mm), and the peripheral area (inner diameter of 3 mm and an outer of 6 mm). The mean thickness at the intersections point of six radial scans from the eyes was used for analysis. Total macular volumes (TMV) of the patients detected by OCT also obtained.

Only one eye of each subject was chosen randomly for all subsequent analyses in this report.

The study was approved by the local ethical committee and performed according to the World Medical Association of Helsinki Declaration. Written informed consent was obtained from all parents.

Statistical analysis

Results were expressed as means ± standard deviations (SDs), and percentages with 95% confidence intervals. Descriptive statistics, Student's *t*-test, Mann–Whitney U-test, Chi-square test for comparison of the group parameters and correlation analyses (Spearman analysis) were performed with SPSS statistical software 17.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set to $P < 0.05$. Furthermore, the influence of duration of diabetes and HbA1c on IOP, CCT, Schirmer test, BUT, TMV, central retinal thickness (CRT) was investigated by a multivariate regression using the same software.

Results

The mean age of the patients with diabetes was 13.2 ± 3.1 years (mean ± SD, range: 4–18 years). The mean age of the healthy subjects was 13.26 ± 2.6 years (range 7–18 years).

Twenty patients were male in diabetic group (47.6%), and 21 patients were female in control group (50%). The mean duration of diabetes was 3.6 ± 3.1 (median was 3 years) and mean HbA1c value was 9.7% ± 2.4% in the diabetic group. All eyes included in the analysis had a visual acuity of at least 20/20. IOP was 16.7 ± 2.9 mmHg in diabetic group and 14.7 ± 2.5 mmHg in the control group. Even though there was no diagnosis of glaucoma, IOP measurements were found significantly higher in the diabetic group than in the control group ($P = 0.001$) [Table 1]. Schirmer test was found to be 15.5 ± 3.9 mm in diabetic group and 19.8 ± 3.9 mm in the control group. There was statistically significant difference between diabetic and control group for the Schirmer test values ($P < 0.001$). BUT was 13.3 ± 3.3 s in the diabetic group and 12.0 ± 1.8 s in the control group. There was no statistically significant difference between the diabetic and control group for the BUT (P = 0.182); for the CCT (P = 0.495). TMV values were 6.68 ± 0.637 mm^3 and 7.02 ± 0.483 mm^3 in diabetic and control group, respectively (P = 0.007). CRT values were 161.31 ± 27.837 μm and 191.26 ± 15.33 μm in diabetic and control group, respectively ($P < 0.001$). The measurements of TMV and CRT were found significantly lower in the diabetic

Table 1: Descriptive data from the diabetic and control groups

	Diabetic group	Control group	*P*
Mean age	13.2±3.096	13.3±2.614	0.939
IOP	16.7±2.9	14.7±2.553	0.001
Schirmer	15.5±3.94	20.9±3.805	<0.001
BUT	13.3±3.271	12.1±1.76	0.182
CCT	555.4±41.22	561.5±39.7	0.495
TMV	6.68±0.637	7.02±0.483	0.007
CRT	161.31±27.837	191.26±15.33	<0.001

Statistically significant difference $P<0.05$, mean±SD. IOP: Intraocular pressure (mmHg), BUT: Tear break-up time (s), CCT: Central corneal thickness (μm), TMV: Total macular volume (mm^3), CRT: Central retinal thickness (mean thickness at intersection point of 6 radial scans, μm), SD: Standard deviation

group than in the control group ($P < 0.05$) [Table 1]. There was only one patient who was diagnosed as preproliferative DR with retinal microaneurysms, cotton wool spots, flame-shaped hemorrhages without neovascularization.

In the diabetic group, the univariate regression analysis showed a statistically significant negative correlation between HbA1c and CCT ($R = -0.297$, $P = 0.017$). We analyzed the correlation between the age, duration, HbA1c and IOP, BUT, Schirmer test, TMV, CRT measurements in the diabetic group but the correlations did not reach statistical significance [Table 2].

Discussion

DM as a systemic disease has several well-known ocular complications including anterior and posterior segment such as DES, glaucoma, corneal pathologies, and retinopathy. In the current study, we checked the metabolic status of Type 1 DM children with a full anterior and posterior segment ophthalmologic examination and compared the results with sex- and age-matched healthy controls.

Annual screening starting at the age of 10 is recommended for all diabetic patients.[13,14] The mean age of the diabetes group was 13.21 ± 3.096 ranging from 4 to 18 years in this study.

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.[15] 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. Diabetic sensory neuropathy of the cornea may play a role in decreased tear secretion. Although some found an increased risk for dry eye among diabetic individuals,[16] others did not find a significant decrease in the amount of aqueous tear flow and tear BUT among insulin-dependent diabetic patients.[16]

In this study, no DES was reported regarding BUT and Schirmer test, and there was no significant difference for BUT between the diabetic group and nondiabetic control group. BUT is a well-known easily performed test for the determination of tear film stability. Even though it is performed in a standardized procedure, large deviations between individuals and also within the individuals can be found. Thus, if no significant differences were found between diabetic and nondiabetic subjects regarding tear film BUT, it cannot be concluded from these data that tear film stability does not actually differ between diabetics and nondiabetics.[17]

We found that Schirmer test values were significantly lower in diabetics than in nondiabetic children. Our results showed that the basic tear flow in diabetics might be altered. Many studies reported that reflex tear secretion was mainly affected in diabetics because of the corneal sensory neuropathy along with microvascular damage of the lacrimal gland. Schirmer test when performed in a standardized procedure, the finding of a statistically significant difference may provide valuable information on the amount of tear secretion.[15]

Goebbels found neither a significant decrease in the amount of aqueous tear flow nor an impaired tear BUT among insulin-treated diabetic patients. They reported that Schirmer test readings were significantly decreased, and there were more signs of conjunctival metaplasia.[17] One of the limitations of this study is a lack of impression cytology of the conjunctival surface, which may show signs of conjunctival metaplasia in diabetic children. However, this method may not be useful in children.

In this study, we could not find any correlation between the glycemic control (HbA1c) and BUT, Schirmer test readings. Some studies reported that the severity of DES correlated with the severity of DR, which is well-known to correlate with glycemic control.[18,19]

In contrast, Binder *et al*.[20] reported that sicca symptoms affected some Type 1 diabetic patients only during the hyperglycemic phases. They concluded that this could result from high extracellular fluid osmolarity disturbing tear production, rather than represent a chronic complication of diabetes.

In this study, we found statistically significant difference for IOP between the diabetic and nondiabetic groups. It is currently not known whether the biomechanics of the cornea are altered in diabetes dependent on the diabetic metabolic state. In our analysis, there was no significant difference for the CCT between two groups. Our study showed that there was a negative but weak correlation between the HbA1c and CCT. There are some studies associating diabetes with thicker corneas[7,8] and IOP.[10] In a study, CCT correlated significantly with HbA1c. They explained that increased corneal thickness in patients with diabetes might be related with the alteration of the ground substance, in particular, the glycosylation of proteoglycans and glycosaminoglycans.[21] In the same study, IOP was found to be higher in patients with diabetes compared to controls as in our report. This finding might be caused by the alteration of the biomechanical properties of the cornea related with diabetes affecting the IOP measurement. This higher corneal resistance could lead to a falsely high IOP measurement. In addition, Last *et al*. hypothesized that an elevated corneal resistance factor owing to diabetes is accompanied with changes of the trabecular meshwork leading to an IOP increase.[22] Despite

Table 2: Correlation analysis of intraocular pressure, Schirmer test, central corneal thickness, tear break-up time, total macular volume, central retinal thickness, and diabetes mellitus-related variables

	IOP		Schirmer		CCT		BUT		TMV		CRT	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Duration	0.2	0.08	0.03	0.81	0.085	0.442	−0.07	0.52	−0.01	0.948	−0.12	0.266
HbA1c	−0.15	0.16	0.14	0.21	−0.291	0.007	0.09	0.41	0.111	0.314	0.014	0.897

Statistically significant difference $P < 0.05$. *R*: Correlation coefficient, IOP: Intraocular pressure (mmHg), BUT: Tear break-up time (s), CCT: Central corneal thickness (μm), TMV: Total macular volume (mm^3), CRT: Central retinal thickness (mean thickness at intersection point of six radial scans, μm), HbA1c: glycosylated hemoglobin

our study, another study showed that the diabetic children without retinopathy had an IOP which was equal to that of a control group of nondiabetic children. The same study revealed that the diabetic children with retinopathy had a significant elevation of their IOP.[23] In the present study, we found that the prevalence of DR in a group of young diabetic patients attending pediatric endocrinology clinics was 2.4%. There was only one patient who was diagnosed as preproliferative DR with retinal microaneurysms, cotton wool spots, flame-shaped hemorrhages without neovascularization. This prevalence is low compared to that reported in previously published studies[2,3,24] which ranged from 5% to 50%. The difference may be due to several factors, including the methods used to screen for DR, the type of population screened, the age of the patients, and the duration of diabetes. In this study, diabetic patients had a lower mean HbA1c measurement (9.7% ± 2.4%) than those of reported in the literature.[2,3,24,25] In addition, 23.8% of our young patients had a HbA1c below 8%, and 26.2% of the patients had diabetes more than 5 years. Compared to the previous series, our patients had shorter diabetes duration, which may explain their lower DR prevalence. The detection of DR is very important because the presence of preproliferative (mild) DR may be a risk factor for progression towards more severe forms. According to Maguire *et al*., this may not apply to young children, in whom mild DR may regress spontaneously.[26] However, spontaneous improvement of DR is less likely to occur in older children and adolescents. The presence of mild DR in groups of young diabetic patients at higher risk, whose HbA1c exceeds 10% and whose diabetes duration is longer than 10 years, should be screened frequently.[24] Our patient with preproliferative DR had diabetes for 12 years, and his HbA1c was 11.9%. He was advised for a frequent retinal screening program by fundus photography. Even if most of these early retinal changes found in diabetic children do not need any therapy, it is important to diagnose retinopathy as soon as possible after the first signs to intensify treatment for a controlled metabolic status, to prevent and delay further development of retinopathy.[27]

Longer duration of diabetes and poorer glycemic control have been reported as independent risk factors for DR in children and adolescents.[2,28] The decrease in DR prevalence reported in recent studies[24] was observed despite a persistently high mean HbA1c, which was higher than the HbA1c recommended by the Diabetes Control and Complications Trial.[27] However, most young diabetic patients are now treated with either multiple injections or insulin pumps as in our study. Therefore, as suggested by Mohsin *et al*.[29] the lower prevalence of DR observed in most recent studies may be partly due to fewer glucose excursions.

This study revealed that there was a significant difference for the TMV and CRT between the diabetic and nondiabetic groups. The TMV and CRT measurements of control group were significantly higher than the diabetic group. In a recent study, the retinal thickness was found to be decreased in subjects with DM Type 1 and minimal DR compared with healthy controls.[12] Two studies have suggested that patients with DM and no retinopathy have retinal thickness values that are similar to values from populations without diabetes and a normal retina.[30,31] The loss of retinal thickness in the early phase of DR may be explained by a loss of neural tissue, and this is supported by several reports on apoptosis of neuroglial tissue in DM and subtle changes in retinal function observed in DM before the development of DR.[12,31]

This study has several limitations. First, our study had a small sample size. The prevalence of DR in this study is based on just one patient. Second, this is a cross-sectional study, and therefore, it is difficult to determine the effects of timing on measurements. Third, a selection bias could have affected the results because of consecutive selection manner, though its impact on the results is uncertain. Therefore, further studies with larger sample sizes, including more factors related to DM complications, are needed in the future.

The strength of our study compared to other studies is the strict inclusion of patients with Type 1 DM only. Our study group, with a well-known duration of patient's disease, is a more homogeneous compared to a mix of Type 1 and Type 2 patients as used in other studies.[32,33]

Our findings strengthen the need for more frequent screening for the diabetic complications, including neuropathy-related DES, IOP changes, and DR.

Conclusions

Type 1 DM group exhibited significantly reduced Schirmer test, increased IOP and decreased retinal thickness relative to the age-matched control group. Children with Type 1 DM may be at a greater risk of diabetic neuropathy and retinopathy which may progress to visual disturbances and even blindness unless detected and treated in time.

More frequent screening might be helpful for early diagnosis of complications, including neuropathy-related DES, IOP changes, and DR.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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