Evaluation of Ocular Parameters in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Objective: *The aim of this study was to investigate the effect of childhood Type 1 diabetes (DM) on ocular parameters.*

Subjects and methods: *Forty-six children with Type 1 DM without diabetic retinopathy (Group 1) and 76 healthy children (Group 2) were included in the study. Routine eye examinations and fundus photography were performed. Central corneal thickness (CCT), contract ultrasonic pachymetry and intraocular pressure (IOP) were measured. Retinal nerve fibre layer (RNFL) thickness was measured in four separate quadrants. Central 1-mm maximum retinal thickness and minimum full retinal thickness at the foveal pit (MFRT) were measured with the same Fourier-domain optical coherence tomography. Data for the two groups were then compared.*

Results: *One hundred thirty-five children were included. Mean CCT and IOP values did not differ significantly between the groups (*$p > 0.05$*). Minimum foveal thickness (*$p < 0.05$*) and MFRT (*$p = 0.008$*) measurements in Group 1 were significantly lower compared to those in Group 2. No significant difference was determined between the groups in terms of mean, inferior, superior, nasal or temporal MFRT (*$p > 0.05$*).*

Conclusion: *Variations may arise in IOP and CCT in children with Type 1 DM. Neurodegenerative processes in the retina may begin before the onset of diabetic retinopathy.*

Keywords: Child, contamination, diabetes, ocular parameters

Evaluación de Parámetros Oculares en los Niños con Diabetes Mellitus Tipo 1

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RESUMEN

Objetivo: *El objetivo de este estudio fue investigar el efecto de la diabetes tipo 1 (DM) en los parámetros oculares en la niñez.*

Sujetos y métodos: *En el estudio se incluyeron cuarenta y seis niños con DM tipo 1 sin retinopatía diabética (Grupo 1) y 76 niños sanos (Grupo 2). Se realizaron exámenes oculares de rutina y fotografías de fondo de ojo. Se midieron el espesor corneal central (ECC), paquimetría ultrasónica y la presión intraocular (PIO). El espesor de capa de fibras ner-viosas de la retina (CFRN) se midió en cuatro cuadrantes separados. El espesor foveal central mínimo (EFCM) de 1 mm y el espesor retiniano completo mínimo en el pozo foveal (ERCM) se midieron con la misma tomografía de coherencia óptica en el dominio de Fourier. Luego se compararon los datos de los dos grupos.*

Resultados: *Se incluyeron treinta y cinco niños. Los valores promedio de ECC y PIO no difirieron significativamente entre los grupos (*$p > 0.05$*). Las mediciones del espesor foveal mínimo (*$p < 0.05$*) y ERCM (*$p = 0.008$*) en el Grupo 1 fueron significativamente más bajas en compa-*

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ración con las del Grupo 2. No se determinaron diferencias significativas entre los grupos en términos de ERCM medio, inferior, superior, nasal o temporal (p > 0.05).
Conclusión: *Pueden presentarse variaciones en la PIO y el ECC en los niños con DM tipo 1. Los procesos neurodegenerativas en la retina pueden comenzar antes de la aparición de la retinopatía diabética.*

Palabras claves: niños, contaminación, diabetes, parámetros oculares

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic childhood diseases. The prevalence of diabetes in children has been increasing worldwide in recent years (1, 2). While it is seen in all age groups, it is most common at ages 7–15 years (3, 4). Genetic, environmental and autoimmune factors are involved in the aetiology (3). Although diabetes is treatable, macro- and microvascular complications involving several systems may be seen in the course of the disease. Macrovascular complications are classified as coronary heart disease, cerebrovascular disease and peripheral arterial disease, while microvascular complications include retinopathy, nephropathy and neuropathy (5).

In ophthalmological terms, cataract, anterior ischaemic optical neuropathy, extraocular nerve palsy, diabetic papillopathy, and primary and neovascular glaucoma are more common in patients with diabetes (6–11). Diabetic retinopathy, which is not widespread in children with Type 1 diabetes, is one of the leading causes of blindness between the ages of 20 and 74 years in developed countries (3). Loss of vision in patients with diabetes can be prevented by detecting diabetic retinopathy in the early-stages. Apoptosis in neuronal and glial cells has been observed in very early-stage retinopathy in human and animal studies (12–14).

In assessing ocular findings in diabetes, detailed anterior and inferior segment examination must be performed and intraocular pressure (IOP) must be measured. Studies have reported that central corneal thickness (CTT) is an important parameter in the detection and treatment of glaucoma and that low CTT is a risk factor for glaucoma (15–19). Various instruments are used to measure IOP. The Goldmann tonometer is still the gold standard in CTT measurement (20, 21). Optical coherence tomography (OCT) is an important diagnostic imaging technique in pathologies in the retina that are difficult to determine using fundoscopy, and provides high-definition images, particularly in terms of retinal diseases and glaucoma (22, 23).

The purpose of this study was to investigate the effects of childhood Type 1 diabetes on ocular parameters.

SUBJECTS AND METHODS

Children being treated for Type 1 diabetes without diabetic retinopathy on an outpatient basis at the Erzurum Regional Education and Research Hospital Pediatric Endocrinology Clinic during 2013 to 2014 and healthy children were included in the study. The study was performed in a prospective, controlled manner. Erzurum Regional Education and Research Hospital Ethical Committee approval in line with the Helsinki Declaration was obtained before the study began. Children whose parents returned informed consent forms were included. All ophthalmological examinations were performed by the same ophthalmologist (OOO). Children were given routine ophthalmological examinations. Fundus photography was performed after the pupil was dilated with 0.5% phenylephrine hydrochloride and 0.1% tropicamide. Subjects with corneal pathology, contact lens users, with a history of intraocular surgery and those using topical ocular drugs were excluded. We also ensured that children included in the study had no ophthalmological or systemic disease that might affect retinal nerve fibre layer (RNFL) and retinal thickness.

Intraocular pressure and central corneal thickness measurement

Intraocular pressure was measured in suitable children under topical anaesthesia (proparacaine HCI 0.5%) using Goldmann applanation tonometry (GAT, Haag Streit, Koeniz, Switzerland), and CTT using contact ultrasonic pachymetry (Pacline Opticon 2000, Spa Vicadel Casale

di Settebagni, 1300138 Rome-Italy), at least three times for each eye. The lowest CTT value was selected.

Optical coherence tomography measurement

The RTVue-100 OCT (Optivue, Inc, Fremont, CA, USA) is a new generation A-Scan OCT instrument Fourier-domain (FD) with an axial resolution of 5 μ and scanning speed of 26000/sec. Optic nerve fiber layers, retinal thickness in a 1 mm-diameter circular region at the fovea (MRT) and minimum full retinal thickness at the foveal pit were measured using RTVue-100 after pupillary dilation. The optic nerve head (ONH) protocol consists of 12 radial scans, 3.4 mm in length and six concentric ring scans ranging from 2.5 to 4.0 mm in diameter all centered on the optic disk. The ONH protocol also generates a polar RNFL thickness map, measured along a circle 3.45 mm in diameter centred on the optic disk. It gives the average RNFL thickness in the temporal, superior, nasal and inferior quadrants as well as the overall average along the entire measurement circle.

The MM5 protocol was performed for RTVue measurements. The protocol consists of a dense 5 × 5 mm grid of linear scans around the macula. Protocols of the RTVue-100 (version 2.0), the MM5, was used. The MM5 protocol performs faster scans which include: 12 horizontal and 12 vertical scans at 0.5 mm intervals. Each line scan consists of 512 A-scans over a 5 mm scan length. Average retinal thickness in a 1 mm-diameter circular region at the fovea (MRT) and minimum full retinal thickness (MFRT) at the foveal pit were obtained using the EMM5 software for the RTVue-100.

Statistical analysis

Data were analysed on SPSS 20.0 software. One-way analysis of variance (ANOVA) was used to compare descriptive data. Pearson's Chi-squared test was used to compare qualitative data. Correlations between parameters were analysed using Pearson correlation analysis. Significance was set at $p < 0.05$.

RESULTS

Forty-six children with DM but no diabetic retinopathy (Group 1) and 67 healthy children (Group 2) were included in the study. The groups' descriptive characteristics (age, weight, height, gender distribution) are shown in Table 1. No significant difference was determined between the groups in terms of mean and gender ($p > 0.05$). Mean height, weight and HbA_{1c} measurement were significantly higher in Group 1 than in Group 2 ($p < 0.05$).

Mean CTT was 574.5 ± 37 μm in children with diabetes and 569.5 ± 35 μm in the healthy children. Mean IOP was 16.5 ± 3.1 mm Hg in diabetic children and 15.3 ± 3.2 mm Hg in the healthy subjects. Although mean CTT and IOP were higher in the diabetic children, the difference was not significant ($p > 0.05$). The groups' optic nerve and retinal parameters are given in Table 2.

Table 1: Comparison of groups' demographic characteristics

	Diabetic group n = 46	Healthy group n = 67	*p*
Gender (F/M)	28/18	41/26	> 0.05
Age (years)	12 ± 3.1	12.3 ± 2.9	> 0.05
Height (cm)	141.1 ± 15.4	144 ± 13.2	< 0.05
Weight (kg)	55.13 ± 5.8	38 ± 4.7	< 0.05
HbA_{1c}	9.3 ± 2.6	4.5 ± 1.1	< 0.05

HbA_{1c}; Haemoglobin

Table 2: Groups' optic nerve and macular thicknesses, central corneal thickness and intraocular pressure values

	Diabetic group n = 46 Mean ± SD	Healthy group n = 67 Mean ± SD	*p*
Nasal RNFL, μn	81.9 ± 9.2	78 ± 12.6	*> 0.05*
Temporal RNFL, μn	81.6 ± 10.1	80.9 ± 11.4	*> 0.05*
Superior RNFL, μn	137.6 ± 17.1	134.8 ± 19	*> 0.05*
Inferior RNFL, μn	139.9 ± 16	140.1 ± 19.2	*> 0.05*
Mean RNFL, μn	110 ± 10.9	108 ± 11.8	*> 0.05*
MRT, μn	225.08 ± 11.04	235.62 ± 23.07	*0.043**
MFRT, μn	183.56 ± 26.84	199.95 ± 25.72	*0.008***
CTT (μm)	574.5 ± 37	569.5 ± 35	*> 0.05*
IOP (mm Hg)	16.56 ± 3.1	15.2 ± 3.2	*> 0.05*

RNFL: Retinal nerve fibre layer, MRT: minimum retinal thickness in a 1 mm-diameter circular region at the fovea, MFRT: Minimum full retinal thickness at the foveal pit, CTT: central

No significant difference was determined between the groups in terms of mean, nasal, temporal, superior or inferior RNFL thicknesses. Central 1 mm foveal thickness ($p < 0.05$) and minimum full retinal thickness at the foveal pit ($p < 0.01$) were significantly lower in Group 1 than in Group 2.

DISCUSSION

To the best of our knowledge, all previous studies of macular thickness and Type 1 DM have involved the adult age group, while the significant aspect of this study is that it was performed with children. Central foveal thickness and minimum foveal thickness values were sig-

nificantly low in children with Type 1 DM without diabetic retinopathy, while RNFL values were not significant. Retinal thickness values may have decreased in this study in association with intraretinal neuronal cell loss without microaneurysm or haemorrhage, in other words, without vascular changes. Interestingly, intraretinal neuronal cell loss occurred in children with DM without development of diabetic retinopathy. Previous studies report differing opinions regarding diabetic retinopathy-related retinal thickness. One suggestion is that hyperglycaemia causes serum protein and lipid accumulation in the intraretinal space in diabetic patients by increasing vascular permeability. This may result in diabetic patients exhibiting higher retinal thickness values compared to controls (24). A second hypothesis is that while intraretinal nutrition occurs through retinal circulation, the retina is nourished externally through choroidal circulation. Therefore, high metabolites do more damage to the inner retina. Insulin is a protective factor for the retinal nerves, while apoptosis may occur in retinal tissue in association with hyperglycaemia and toxic material deposition associated with decreased insulin sensitivity (25, 26).

Intraretinal neuronal cell losses may therefore be seen without vascular changes in early-stage diabetic retinopathy. This may lead to a decrease in retinal thickness. Few studies have investigated macular thickness and optic nerve parameters in patients with Type 1 DM. One study of 55 adults with Type 1 DM, with or without diabetic retinopathy, reported no significant difference in foveal thickness values compared to those of the control group, but determined significantly lower foveal thickness in DM patients with minimal diabetic retinopathy compared to the control group. This was potentially attributed to neuron loss inside the retina in the early-stage of diabetic retinopathy (27). Another study reported significantly greater central foveal thickness in patients with DM with no diabetic retinopathy compared to a healthy control group. It suggested that this represented an early finding of diabetic retinopathy.

Hyperglycaemia causes serum protein and lipid accumulation in the intraretinal space in diabetic patients by increasing vascular permeability. Higher CTT values have therefore been reported in diabetic patients than in healthy controls (28). Van Dijik *et al* (29) reported significantly low ganglion cell layer and mean RNFL values in patients with Type 1 DM with minimal diabetic retinopathy and suggested that this might be due to neurodegenerative processes associated with early-stage diabetic retinopathy. One study from 2012 determined significantly elevated perifoveal thickness in patients with DM with no diabetic retinopathy, but detected no signifi-cant difference in terms of central foveal thickness compared to the control group. Mean and inferior RNFL thickness values were also significantly high (30).

Epithelial and endothelial cells may be seen in association with diabetic keratopathy as well as diabetic retinopathy.

Corneal epitheliopathy-related punctuate keratitis and decreased adhesion in the basal membrane may be seen. Changes in endothelial cells associated with alterations in the endothelium and endothelial thickening associated with endothelial pump function compromise may be seen (31, 32). A positive correlation was determined between CTT and IOP in our study. In addition, mean CTT and IOP were higher in diabetic children than in the healthy controls, although the difference was not significant.

Lee *et al* (33) reported that corneal thickness and corneal pattern changes were significantly correlated with length of disease in patients with diabetes for 10 years or longer. Keolain *et al* (34) determined abnormal changes in the corneal endothelium, although function was not affected. In another study, although diabetic cornel thickness was significantly high, no significant correlation was determined between CCT and duration of diabetes (35). Morphological changes may occur in diabetic patients due to impairment of the Na+-K+ ATPase pump and changes in corneal permeability may result in corneal thickening according to another study (36).

A study of children and adolescents with Type 1 DM reported significantly higher CCT in diabetic adolescents compared to healthy controls. That study emphasized the importance of assessing the endothelium in diabetic patients using a specular microscope (37). Central corneal thickness was significantly higher in diabetic children and adolescents compared to healthy controls in another study, and duration of diabetes was proposed as a significant factor (38). Another study of children with Type 1 diabetes determined significantly higher CCT in diabetic children compared to controls and mentioned a correlation between duration of diabetes and CCT (39). Another study involving patients with Type 1 and Type 2 diabetes in adult age groups reported significantly higher CCT in diabetic patients but determined no significant correlation between duration of diabetes and increased CCT (36). Few studies have investigated IOP in children with Type 1 diabetes. One study comparing IOP in children with Type 1 diabetes and healthy children reported that Type 1 diabetes did not significantly increase IOP

(40). Another study, however, reported significantly higher IOP in children with diabetic retinopathy compared to those with no diabetic retinopathy and a healthy control group (41).

Although the low number of diabetic cases may appear to be a limitation of this study, this research still provides a broad perspective in terms of the parameters investigated. In conclusion, this study is significant in being the first to investigate children with Type 1 diabetes in terms of macular thickness and RNFL values. In addition, IOP and CTT should be routinely measured in diabetic children in order to avoid serious glaucoma-related complications.

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