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Evaluation of Corneal Endothelium and Central Corneal Thickness in Children and Adolescents with Type 1 Diabetes

Tip 1 Diyabetli Çocuk ve Adölesanlarda Korneal Endotel ve Santral Kornea Kalınlığının Değerlendirilmesi

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ABSTRACT

Background: To evaluate whether corneal endothelium and central corneal thickness (CCT) changed in children and adolescents with type 1 diabetes (T1D) without clinical signs of diabetic retinopathy (DR).

Materials and Methods: This retrospective, cross-sectional, observational clinical study evaluated consecutive children and adolescents with T1D without DR between January 2020 and February 2021. Quantitative data of endothelial cell density (ECD), CCT, polymegathism, and pleomorphism rates of endothelial cells were recorded using a non-contact specular microscope; they were compared with those of healthy peers, and whether they were significantly associated with puberty stage, duration of diabetes, and median HbA1c level was investigated.

Results: The study included 112 eyes of 56 patients in the T1D group and 92 eyes of 46 subjects in the control group. Mean age was 12.2±3.2 (6-18) years and mean duration of diabetes was 3.4±2.4 (1-12) years. Mean ECD was significantly lower (p=0.012) and mean CCT was higher (p=0.004) in the T1D group compared to the control group. Mean ECD was significantly lower in females with T1D (3028±292) than in males with T1D (3080±233) (p=0.048). From prepubertal to postpubertal stages, mean ECD significantly decreased whereas mean polymegathism increased. The age and puberty stage were negatively correlated with ECD and CCT and significantly positively correlated with polymegathism (p<0.05).

Conclusion: Corneal endothelial changes begin early even if the duration of diabetes is short in children and adolescents with T1D without DR. ECD is lower in females with T1D than in males with T1D; therefore, the impact of sex should be considered.

Keywords: Endothelial cell density, pediatric type 1 diabetes, pleomorphism, polymegathism, specular microscope

ÖZ

Amaç: Diyabetik retinopatinin (DR) klinik belirtileri olmayan tip 1 diyabetli (T1D) çocuk ve adölesanlarda korneal endoteli ve santral kornea kalınlığının (SKK) değişip değişmediğini değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif, kesitsel, gözlemsel klinik çalışmada, Ocak 2020 ile Şubat 2021 arasında DR'siz T1D'li çocuk ve adölesanlar ardışık olarak değerlendirildi. Endotel hücre dansitesi (EHD), SKK, polimegatizm ve endotel hücrelerinin pleomorfizm oranlarına ilişkin kantitatif veriler non-kontakt speküler mikroskop kullanılarak kaydedildi; hastalar sağlıklı yaşıtlarıyla karşılaştırıldı ve verilerin puberte evresi, diyabet süresi ve medyan HbA1c düzeyi ile anlamlı bir ilişkisi olup olmadığı araştırıldı.

Bulgular: Çalışmaya T1D grubunda 56 hastanın 112 gözü ve kontrol grubunda 46 kişinin 92 gözü dahil edildi. Ortalama yaş 12,2±3,2 (6-18) yıl ve ortalama diyabet süresi 3,4±2,4 (1-12) yıldı. Kontrol grubuna göre T1D grubunda ortalama EHD anlamlı olarak daha düşük (p=0,012) ve ortalama SKK anlamlı olarak daha yüksekti (p=0,004). Ortalama EHD, T1D'li kadınlarda (3028±292) T1D'li erkeklerden (3080±233) anlamlı olarak daha düşüktü (p=0,048). Prepubertalden postpubertal aşamalara, ortalama EHD önemli ölçüde azalırken, ortalama polimegatizm artış gösterdi. Yaş ve puberte evresi EHD ve SKK ile negatif, polimegatizm ile anlamlı pozitif korelasyon gösterdi (p<0,05).

Sonuç: DR'si olmayan T1D'li çocuk ve adölesanlarda diyabet süresi kısa olsa bile korneal endotel değişiklikleri erken başlamaktadır. EHD, T1D'li kadınlarda, T1D'li erkeklerden daha düşüktür; bu nedenle, cinsiyetin etkisi dikkate alınmalıdır.

Anahtar Kelimeler: Endotel hücre yoğunluğu, pediatrik tip 1 diyabet, pleomorfizm, polimegatizm, speküler mikroskop

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Introduction

There has been a tremendous increase in the incidence of type 1 diabetes mellitus (T1DM) in children and adolescents in the last decade (1). T1DM is a chronic disease with microvascular complications such as retinopathy, neuropathy and nephropathy. The most common eye complication of T1DM is diabetic retinopathy (DR) (2). Further, complications may develop not only in the posterior segment but also in various layers of the cornea, which are components of the anterior segment (3).

The corneal endothelium consists of amitotic, hexagonal, single-layer endothelial cells. These cells regulate corneal hydration and maintain corneal transparency (4). However, their number decreases over time owing to aging or various diseases, including T1DM. Consequently, adjacent endothelial cells expand. This results in an endothelium with enlarged (polymegathism) and non-hexagonal (pleomorphism) cells; further, the central corneal thickness (CCT) increases as a result of corneal hydration (4,5). Finally, if the endothelial cell density (ECD) decreases below a certain value, the cornea may become edematous and hazy, causing a decrease in vision (4). The ECD is very important in the continuation of corneal transparency in pediatric T1DM patients for their advanced ages because endothelial cells gradually decrease in number and are amitotic. Studies investigating corneal endothelial cell variables in children and adolescents with T1DM are scarce (6,7,8,9).

The current study aims to evaluate whether the ECD, polymegathism, and pleomorphism rates of endothelial cells as well as the CCT change in children and adolescents with T1DM. Secondary aims were to assess wether an association exist between the specular microscopy variables and demographic and clinical characteristic and median HbA1c levels representing the last year of follow-up.

Material and Methods

This study was approved by the Local Human Research Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 2444, date: 25/06/2019). Informed consent was obtained from all the legal guardians or parents. Assent was also taken from subjects over seven years of age.

Study Participants

This retrospective, cross-sectional observational study included pediatric subjects with T1DM without clinical sign of DR from the outpatient clinic of pediatric diabetes who were evaluated between January 2020 and February 2021. Healthy controls were obtained from individuals who were examined in the outpatient ophthalmology clinic for routine evaluation. Because the right and left eye measurement values of the same case were different from each other, the right and left eyes of cases were evaluated.

Patients' age (years), gender, duration of diabetes, body mass index (BMI), and yearly median levels of HbA1C (%) were recorded. The pubertal stage was evaluated using the Tanner and Whitehouse (10) method. None of the enrollees had microvascular diabetic complications of diabetes.

Ophthalmological examinations of all cases were performed by one and the same ophthalmologist (S.T.D.), including non-cycloplegic refraction measurements (Topcon KR-800 Auto Kerato-Refractometer, Japan), best corrected visual acuity (BCVA), biomicroscopy, fundoscopy, and intraocular pressure measurements.

Patients were included in this study if they had 20/20 BCVA according to the Snellen chart, cylindrical or spherical refractive errors ⩽3 diopter (D), no systemic disease other than T1DM, no sign of DR on fundoscopy, age of 7-18 years, positive antibodies against anti-insulin, and/or islet cells (anti-ICA) and/or glutamic acid decarboxylase (anti-GAD) at presentation, diabetes duration of at least 1 year and could provide head position during ocular imaging. The control group consisted of healthy volunteer peers with 20/20 BCVA according to the Snellen chart, no other ocular or systemic disorder, and cylindrical or spherical refractive errors ⩽3 D.

Those with any of the following conditions were excluded: Children with a history of ocular surgery or trauma or used contact lenses, intraocular inflammation, age less than 7 years or more than 18 years, cylindrical or spherical refractive errors >3 D, increased intraocular pressure, smoking, presence of any systemic disease other than T1DM, and who were unable to cooperate during the ocular examination.

In specular microscopy imaging, patients were told to look toward the fixation target. Specular microscopy measurements were repeated until three consecutive compatible measurements were obtained, and the best-quality image was analyzed.

The ECD (cells/mm^2), percentage of polymegathism rates of endothelial cells, CCT, and percentage of hexagonal cells (pleomorphism) were evaluated with a non-contact specular microscope (CEM-530, Nidek Co, Japan) in all participants. The data of children and adolescents with T1DM were compared with those of their healthy participants. The potential associations of the duration of diabetes, HbA1c level and puberty staging according to Tanner were investigated.

Statistical Analysis

The mean, ratio values, and standard deviation were used to describe the statistics of the data. Data distributions were assessed using the Kolmogorov-Smirnov test. Analysis

of variance (ANOVA; Tukey's test), Mann-Whitney U test, and t-test were used for analyzing quantitative independent data depending on the distributions of the variables being compared. The chi-square test was used to analyze independent data. The correlations were calculated using Pearson's and Spearman's correlational analyses. SPSS 22.0 software was used to conduct statistical analyses. Statistical significance was granted for a p-value <0.05.

Results

The study included 204 eyes of 102 participants; specifically, it included 112 eyes of 56 patients in the T1DM group and 92 eyes of 46 subjects in the control group. Table 1 shows the distribution of age, sex, duration of diabetes, BMI, puberty stage, and median HbA1c level of both groups. Among these variables, there was no significant difference between the two groups in terms of age, sex, BMI and puberty stage (p>0.05 for all).

Table 2 shows the mean specular microscopy variable values of both groups. Compared to the control group, in the T1DM group, the mean ECD values were significantly lower (p=0.012) but the mean CCT values were significantly higher (p=0.004). There was no significant difference between the mean polymegathism and pleomorphism values of both groups (p>0.05 for both).

Table 3 shows the mean specular microscopy variable values according to sex in the T1DM group. The mean ECD value was significantly lower in females with T1DM than in males with T1DM (p=0.048). The mean polymegathism, pleomorphism, and CCT values were not significantly different between females with T1DM and males with T1DM (p>0.05 for all).

Table 4 shows the mean specular microscopy variable values according to puberty stage in T1DM subjects. The puberty stage was significantly associated with mean ECD (p<0.001) and polymegathism (p=0.016) values. From the prepubertal stage to the postpubertal stage, the mean polymegathism value significantly increased but the mean ECD value significantly decreased. As the puberty stage progressed, the mean CCT value decreased, but no statistically significant difference was found (p=0.066).

Table 5 shows correlations between the mean specular microscopy variable values and the mean age, sex, duration of diabetes, HbA1c level, BMI, and puberty stage in the T1DM group. Significant negative correlations were seen between the mean ECD and age (p<0.001) and puberty stage (p<0.001). In other words, as the age and puberty stage progressed, the mean ECD decreased. Further, mean polymegathism showed a significant positive correlation with age (p=0.001) and puberty stage (p=0.001) but a significant negative correlation with sex (p=0.005). Finally, significant negative correlations were seen between the mean CCT and age (p=0.015) and puberty stage (p=0.021).

Discussion

Here we report the results of our study evaluating the ECD, polymegathism, and pleomorphism rates of endothelial cells as well as the CCT effects of diabetes on the cornea via non-contact specular microscopy in pediatric patients with T1DM without clinical DR. Moreover, we assessed the putatively influential association of diabetes duration, median HbA1c level and pubertal status of the enrollees. The mean ECD value was significantly lower in patients with pediatric T1DM compared to healthy children, and the mean CCT value was higher. The mean ECD value was significantly lower in females with T1DM than in males with T1DM. From the prepubertal stage to the postpubertal stage, the mean ECD value significantly decreased, whereas the mean polymegathism value increased. The age and puberty stage showed a significant negative correlation with ECD and CCT but a significant positive correlation with polymegathism.

Diabetes is a fairly common disease that reduces the cellular reserve of the corneal endothelium, thereby causing functional and structural impairments in the cornea (4). Different mechanisms have been proposed in the molecular pathogenesis of changes in the corneal endothelium owing to hyperglycemia. First, in diabetes, Na, K-ATPase activity is reduced; this affects the endothelial pump function and causes the active dehydration of the cornea. Consequently, the thickness of the cornea increases (11,12). Second, the collection of sorbitol and advanced glycation end products (AGEs) in the cornea can cause changes in the endothelial morphology, disturb endothelial cell metabolism, and cause the loss of endothelial cells (13,14). Thus, corneal stromal edema develops and causes cloudy vision (6,15).

The ECD is an indirect indicator of endothelial function and health and is measured using non-contact specular microscopy (4). Previous studies have investigated the potential impact of diabetes on the corneal endothelium and CCT in diabetic adults (9,16,17). However, few studies have evaluated corneal endothelium changes in pediatric diabetics (5,18). Children with diabetes have been reported to have lower ECD and pleomorphism and higher CCT and polymegathism compared to normal children (5,18,19). The effects of local and systemic risk factors such as age, gender, HbA1C level, BMI, and duration of diabetes on corneal endothelial morphology were investigated in pediatric patients with T1DM (5,18). A correlation has been reported between the duration of diabetes and the ECD and CCT (5,18). Anbar et al. (5) and Urban et al. (18)

reported that there was no significant correlation between ECD and CCT on the one hand and age, sex, BMI, and HbA1C level on the other hand in children with T1DM.

In our study, as reported previously, patients with pediatric T1DM had a lower mean ECD value and a higher mean CCT value compared with healthy controls. This may be related to impaired corneal endothelial pump function and accumulation of sorbitol and AGEs in the cornea. To the best of our knowledge, the current study is the first to report a significantly lower mean ECD value in females with T1DM than in males with T1DM. Further, unlike previous studies, we found a significant correlation between age and puberty stage on the one hand and ECD, CCT, and polymegathism on the other hand. However, we found no correlation between the duration of diabetes and CCT and ECD, possibly owing to the shorter mean duration of diabetes in our patients.

Table 1. Demographic and clinical characteristics of children and adolescents with type 1 diabetes and healthy controls

	T1D group (n=56) Mean ± SD or n (54.9%)	Control group (n=46) Mean ± SD or n (45.1%)	p
Age, years	12.2±3.2	11.7±2.9	0.081 X^2
Female/male	31/25	25/21	0.885 X^2
Body mass index, (kg/m^2),	19.8±15	19.1±3.1	0.065 M
The duration of diabetes, years	3.4±2.4	-	
HbA1c level, %	9±2.1	-	
Tanner's puberty stage			
Prepubertal	19	15	0.819 X^2
Pubertal	21	16	
Postpubertal	16	15	

M: Mann-Whitney U test, X^2: Chi-square test, SD: Standard deviation, T1D: Type 1 diabetes

Table 2. The specular microscope variables values in children and adolescents with type 1 diabetes and healthy controls

	T1D group (n=112 eyes) (54.9%) Mean ± SD	Control group (n=92 eyes) (45.1%) Mean ± SD	p
Endothelial cell density	3023±292	3086±233	**0.012** t
Polymegathism	23.94±4.2	24.29±4.7	0.575 M
Pleomorphism	69.24±5.2	68.15±5.7	0.163 M
Central corneal thickness	570.8±34.8	566.1±24.4	**0.004** t

M: Mann-Whitney U test, t: t-test, SD: Standard deviation, T1D: Type 1 diabetes

Table 3. The specular microscope variables values according to sex in children and adolescents with type 1 diabetes

	T1D female (n=62 eyes) (55.3%) Mean ± SD	T1D male (n=50 eyes) (44.7%) Mean ± SD	p
Endothelial cell density	3028±292	3080±233	**0.048** t
Polymegathism	24.47±4.5	23.64±4.4	0.084 M
Pleomorphism	68.54±5.3	69±5.7	0.407 M
Central corneal thickness	567±30.9	570±30.2	0.870 t

M: Mann-Whitney U test, t: t-test, SD: Standard deviation, T1D: Type 1 diabetes

Table 4. The specular microscope variables values according to puberty stage in children and adolescents with type 1 diabetes

	Puberty stage			p
	Prepubertal (n=38 eyes) (34%) Mean ± SD	Pubertal (n=42 eyes) (37.5%) Mean ± SD	Postpubertal (n=32 eyes) (28.5%) Mean ± SD	
Endothelial cell density	3218±312	2948±215	2889±234	**<0.001 A**
Polymegathism	22.8±4.6	23.5±3.2	25.9±4.3	**0.004 A**
Pleomorphism	68.9±5.5	69.8±5	68.9±5.5	0.679 A
Central corneal thickness	580±35.4	568±31.2	561±36.5	0.066 A

A: One-Way ANOVA (tukey test), SD: Standard deviation

Table 5. The correlation data between the demographic and clinical characteristics in the type 1 diabetes group and specular microscope variables values

	ECD		Polymegathism		Pleomorphism		CCT	
	r	p	r	p	r	p	r	p
Age	**-0.478**	**<0.001**	**0.302**	**0.001**	0.031	0.747	**-0.230**	**0.015**
Sex	0.063	0.509	**-0.261**	**0.005**	0.133	0.164	0.075	0.432
Body mass index	-0.088	0.357	0.174	0.067	0.102	0.283	-0.007	0.946
The duration of diabetes	-0.053	0.582	0.019	0.842	0.062	0.517	-0.115	0.226
HbA1c level	0.103	0.279	0.174	0.066	-0.171	0.071	-0.059	0.538
Puberty stage	**-0.456**	**<0.001**	**0.316**	**0.001**	0.049	0.605	**-0.218**	**0.021**

Spearman and Pearson correlation analysis. ECD: Endothelial cell density, CCT: Central corneal thickness

Study Limitations

The current study had many strengths. Unlike previous studies, it only evaluated pediatric patients with T1DM without DR. Sex was found to have a significant effect on ECD. ECD and CCT were found to be significantly and negatively correlated with age and puberty stage. At the same time, this study also had some limitations. Specifically, it included only a limited number of patients, and the median duration of diabetes was relatively short in some enrollees.

Conclusion

Even if the duration of diabetes is short in pediatric patients with T1DM without clinical signs of DR, corneal endothelial changes may begin fpr the early period. When evaluating ECD, the effect of sex should be considered. Non-contact specular microscopy is very useful in detecting these changes. Our findings may serve to highlight the need to do longitudinal follow-up studies to reach hard end-point conclusions regarding whether these cornea-related changes may adversely affect visual function in in pediatric patients with T1DM.

Ethics

Ethics Committee Approval: This study was approved by the Local Human Research Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 2444, date: 25/06/2019).

Informed Consent: Informed consent was obtained from all the legal guardians or parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T.D., A.U., G.K.E., Concept: S.T.D., A.U., G.K.E., Design: S.T.D., S.K.Y., E.B.A.Ö., S.Ü.U., Data Collection or Processing: S.T.D., S.K.Y., E.B.A.Ö., S.Ü.U., Analysis or Interpretation: S.T.D., A.U., G.K.E., S.K.Y., E.B.A.Ö., S.Ü.U., Literature Search: S.T.D., S.K.Y., E.B.A.Ö., Writing: S.T.D., A.U., G.K.E.

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