Evaluation of Retinal Nerve Fiber Layer Thickness with Optical Coherence Tomography in Type 1 Diabetes Mellitus Patients

Tip 1 Diabetes Mellitus'lu Hastalarda Optik Koherans Tomografisi ile Retinal Sinir Lif Tabakası Kalınlığının Değerlendirilmesi

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ABSTRACT Objective: To evaluate retinal nerve fiber layer (RNFL) thickness changes of type 1 diabetes mellitus (DM) patients with and without diabetic retinopathy (DR). **Material and Methods:** One hundred-eighteen patients with type 1 DM and 49 age-matched control subjects were enrolled in the study. Ninety eight of 118 diabetic patients with DR were assigned as group 1 and the remaining 20 patients without DR were labeled as group 20 (n= 98). The RNFL thickness of all subjects were measured using optical coherence tomography (OCT). **Results:** The study included 118 type 1 DM patients with a mean age of 18.77±8.80 years. The mean age of 49 subjects in the control group was 18.71 ± 5.72 (range 7-40) years.The mean RNFL thickness was 103.79 ± 6.45 μm in the control group, 100.00 ± 11.93 μm in group 1 and 85.59 ± 19.81 μm in group 2. The decrease in group 2 was found statistically significant (p< 0.001). The mean RNFL thickness in the superior, nasal, inferior and temporal quadrants were less in group 1 compared to controls, however this data was not statistically significant (p= 0.274, p= 0.149, p= 0326, p= 0783, respectively). In group 2, the RNFL thickness revealed a statistically significant decrease in all quadrants (p< 0.001) except temporal quadrant (p= 0.396). The mean duration of DM was significantly longer in group 2 (153.80 ± 70.35) compared to group 1 (60.76 ± 50.41 months) (p< 0.001). However, there was no correlation between the RNFL thickness and the duration of DM. **Conclusion:** The RNFL thickness of patients with type 1 DM was found less compared to control subjects. This was more prominent in patients with established retinopathy (group 2). These findings suggested that the RNFL thickness measurement with the aid of OCT may be used as an adjunctive diagnostic tool for early diagnosis of DR.

Key Words: Diabetes mellitus, type 1; diabetic retinopathy; tomography, optical coherence

ÖZET Amaç: Diabetik retinopatisi (DR) olan ve olmayan tip 1 diabetes mellituslu (DM) olguların retina sinir lifi tabakası (RSLT) kalınlığı değişikliklerini değerlendirmek. **Gereç ve Yöntemler:** Çalışmaya 118 tip 1 DM olgusu ile yaş yönünden eşleştirilmiş 49 kontrol olgusu alındı. Tip 1 DM olgularından DR'si olan 98 olgu grup 1, ve DR olmayan 20 olgu grup 2 (n= 98) olarak sınıflandı. Tüm olguların RSLT kalınlıkları optik koherens tomografi (OKT) ile ölçüldü. **Bulgular:** Ortalama RNFL kalınlığı kontrol grubunda 103.79 ± 6.45 μm, grup 1'de 100,00 ± 11,93 μm ve grup 2'de 85.59 ± 19.8 μm olarak ölçüldü. Grup 2'deki azalma istatistiksel olarak da anlamlı bulundu (p< 0.001). Superior, nazal, inferior ve temporal kadranlardaki RSLT kalınlığı grup 1'de kontrollere göre daha düşüktü, ancak istatistiksel olarak anlamlı bir farklılık bulunmadı (sırasıyla, p= 0.274, p= 0.149, p= 0.326, p= 0.783). Grup 2'de RSLT kalınlığı temporal kadran hariç (p= 0.396) diğer tüm kadranlarda istatistiksel olarak da anlamlı bir incelme göstermekteydi (p< 0.001). **Sonuç:** RSLT kalınlığı tip 1 DM'li hastalarda kontrol grubuna göre daha düşük bulunmuştur. Bu düşüş retinopatisi olan olgularda daha belirgin hale gelmektedir. Bu bulgular OKT ile yapılan RSLT kalınlığı ölçümünün diabetik retinopatinin erken tanısında yardımcı bir araç olabileceğini düşündürmektedir.

Anahtar Kelimeler: Diabetes mellitus, tip 1; diyabetik retinopati; tomografi, optik tutarlı

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Diabetic retinopathy (DR) is the third cause of blindness in all age groups in developed countries.[1] Poor prognosis of various treatment strategies in advanced diabetic retinopathy has prompted search for alternative methods for earlier detection of DR. The earliest histopathologic changes like pericyte loss in microvascular architecture, basal membrane thickening and endothelial damage are difficult to document in vivo. Therefore, functional changes due to hyperglycemia preceding the ophthalmoscopically detectable findings of DR are of paramount importance.[2] Contrast sensitivity, electrophysiological tests including electroretinography (ERG) and visual evoked potentials (VEP) are some of the established methods to detect early abnormalities attributed to hyperglycemia before the onset of the retinopathy.[3-5]

The optical coherence tomography (OCT), which can quantify retinal changes with a resolution of 8-10 mm, is another alternative technique. It has been widely used to document morphological changes in diabetic macular edema and changes in RNFL thickness in glaucoma patients.[5-7] There are a few studies demonstrating early defects in retinal nerve fiber layer thickness in type 1 and type 2 diabetes mellitus (DM) patients without retinopathy with the scanning laser polarimetry, OCT or fundus photographs, however the results are variable.[8-10] Herein, we conducted a study to provide an answer to these contradictory results and encountered patients with type 1 DM without DR, with DR and age-matched control subjects.

MATHERIAL AND METHODS

The study included patients with type 1 diabetes mellitus and patients who were followed for DR in Selcuk University, Meram Faculty of Medicine, Department of Ophthalmology. Age-matched healthy subjects who visited our clinic with complaints of refractive errors participated in the study as the control group. All patients in the diabetic group and the control group were evaluated for primary open angle glaucoma, ocular hypertension, systemic hypertension, and systemic diseases. Current medical treatment, family history of glaucoma, age and sex was recorded. A comprehensive ophthalmologic examination including best corrected visual acuity, slit lamp examination, applanation tonometry and dilated fundus examination was performed for all patients in the study group and control subjects in Selcuk University, Meram Faculty of Medicine, Department of Ophthalmology. Cup to disc ratio in the optic nerve head was recorded and fundus fluorescein angiography was performed when necessary, and subjects with findings of proliferative diabetic retinopathy were excluded from the study. Subjects with any ophthalmological disorder other than refractive error, patients showing any manifestation of systemic disease other than diabetes mellitus, patients with a history of ocular surgery or photocoagulation treatment, patients under topical and systemic medical treatment, patients with a family history of glaucoma, patients with a best corrected visual acuity under 16/20 and patients with the features of intraocular pressure measurement over 21 mmHg, cup to disc ratio more than 3/10 and an asymmetric cup to disc ratio more than 2/10 were excluded from the study.

Following the above mentioned procedures, informed consent was obtained from all patients and the research was approved by the ethical committee of the Medical Faculty of SelcukUniversity. All subjects underwent RNFL thickness analysis using optical coherence tomography [(OCT-3), (Stratus OCT) Carl Zeiss Meditec, Inc.,CA] by the same doctor (Ş.G.) The measurement procedure involved having the subject seated with his chin in the chin rest and the machine properly aligned following pupil dilatation. The OCT lens was adjusted for the patient's refractive error. The subject was then instructed to fixate the eye on the internal target to enable the examiner to focus on the optic nerve head. The Z-offset was adjusted to the OCT image into view. Polarization was optimized to maximize the reflective signal. The position of the aiming circle was adjusted by the operator to match the optic nerve head. This fast RNFL scan consists of three consecutive circles each consisting of 256 test points along the circle having a diameter of 3.46 mm centered on the optic disc. The RNFL analysis then averages the peripapillary scan

measurements and produces 17 values for each scan set. These include mean RNFL thickness, 4 quadrant averages (superior, inferior, nasal and temporal) and 12 clock-hour averages. Additionally superior maximum (S_{max}), superior average (S_{avg}), inferior maximum (I_{max}), inferior average (I_{avg}) and superior maximum/ inferior maximum (S_{max}) values are presented as a table automatically by the software of the OCT device.

For the analysis of the data, subjects were divided into three groups according to the fundus examination findings. The control group consisted of healthy subjects, group 1 consisted of type 1 DM patients without clinical signs of diabetic retinopathy (DR), and group 2 consisted of type 1 DM patients with non-proliferative diabetic retinopathy.

The data obtained from the right eyes of the participants of each group were transferred into a computer program and statistical analysis was performed using SPSS (Statistical Package for Social Science, Worldwide Headquarters SPSS Inc.) 11.5 Windows package program. The variables were not normally distributed in Kolmogorov-Smirnov test. Thus Kruskal Wallis analysis of variance was used to compare the groups. Post hoc Tukey's HSD was used. A p value of < 0.05 was considered statistically significant.

RESULTS

The study included 118 patients with type 1 DM with a mean age of 18.77 ± 8.80 (range 8-40) years. The mean age of 49 subjects in the control group was 18.71 ± 5.72 (range 7-40) years. Ninety-eight diabetic patients who had no DR in group 1 and 20 patients with DR in group 2 had a mean age of 17.02 ± 8.00 (range 8-38) years and 27.35 ± 7.50 (range 16-40) years, respectively. The difference between the mean ages of control group and type 1 DM group was not statistically significant (p= 0.27). There was also no statistically significant difference between the mean ages of group 1 and control group (p= 0.12). However, the higher mean age of group 2 compared to group 1 and the control group (p< 0.001) was found statistically significant (Table 1). Fifty-four (45.8%) of 118 type 1 DM patients were females and 64 (54.2%) were males. In control group, there were 29 (%59.2) female and 20 (% 40.8) male subjects. There was no significant difference with respect to sex between groups and inter groups (p= 0.263) (Table 1).

TABLE 1: Age and sex distribution.

		Group 1 (n= 98)	Group 2 (n= 20)	Control Group (n= 49)
Age (year) (mean±SD)		17.02 ± 8.00	27.35 ± 7.50	18.71 ± 5.72
Sex	Female	44	10	29
	Male	54	10	20
	p	0.263	0.263	0.263

n= number of patients.

The mean duration of DM was 60.76 ± 50.41 months (mean ± SD) in group 1 and 153.80 ± 70.35 months in group 2. The duration is significantly longer in group 2 (p< 0.001). However, there was no correlation between the RNFL thickness and the duration of DM (p= 0.81).

As RNFL thickness in four quadrants and mean RNFL thickness values were evaluated, slightly smaller measurements were obtained in the mean values of superior, nasal, inferior and temporal quadrants and average thickness values in group 1 compared to the control group, but they were not statistically significant (p= 0.274, p= 0.149, p= 0326, p= 0783, p= 0.241 respectively). In group 2, the mean RNFL thickness in all quadrants and mean RNFL thickness values were remarkably smaller compared to the control group and group 1 except the temporal quadrant which was found to be statistically significant in the analysis (Table 2) (p< 0.001).

Although the S_{max}, S_{avg}, I_{max} and I_{avg} values were slightly smaller in group 1 when compared to the control group, it was not statistically significant (p= 0.559, p= 0.142, p= 0.900, p= 0.498 respectively). In group 2, a further decrease was noted in the S_{max}, S_{avg}, I_{max} and I_{avg} values and was found statistically significant when compared to control group and group 1. There was no statistically significant difference between groups with respect to $S_{max}/I_{max\ value}$ (Table 3).

TABLE 2: RNFL thickness measurements of groups.

RNFL thickness (μm)	Control group (n= 49)	Group 1 (n= 98)	Group 2 (n= 20)	p
Superior	125.57 ± 10.97	121.52 ± 17.65	98.90 ± 30.54	<0.001
Nasal	82.49 ± 12.11	77.60 ± 16.80	61.40 ± 14.64	<0.001
Inferior	135.33 ± 13.19	131.55 ± 18.70	106.75 ± 27.06	<0.001
Temporal	71.88 ± 10.06	70.24 ± 14.98	67.65 ± 22.30	0.396
Mean	103.79 ± 6.45	100.00 ± 11.93	85.59 ± 19.81	<0.001

n= number of patients, RNFL= Retinal nerve fiber layer.

TABLE 3: OCT parameters of groups.

OCT Parameters	Control group (n = 49)	Group 1 (n = 98)	Group 2 (n = 20)	p
Smax (μm)	161.14 ± 14.99	158.08 ± 20.87	131.40 ± 38.62	0.005
Imax (μm)	166.18 ± 17.96	163.96 ± 26.76	139.65 ± 35.75	0.002
Savg (μm)	125.57 ± 10.97	121.52 ± 17.65	98.90 ± 30.54	<0.001
Iavg (μm)	135.33 ± 13.19	131.56 ± 18.68	106.75 ± 27.06	<0.001
Smax / Imax	0.98 ± 0.13	0.97 ± 0.13	0.96 ± 0.26	0.843

OCT: Optical coherance tomography, n=number of patients, S_{max}= Superior maximum thickness, S_{avg}= Superior average thickness, I_{max}= Inferior maximum thickness, I_{avg}=Inferior average thickness.

RNFL and OCT parameters were compared using Kruskal-Wallis among groups to evaluate the significance of the effect of the age. When the age effect in group 2 was ignored, the statistically significant decrease of the average RNFL thickness, RNFL thicknesses determined for all quadrants and other parameters presented in Table 3 was retained in group 2.

DISCUSSION

The complications arising from DM impose an increasing burden on health-care authorities in the world. Although long term effects of DM on vascular architecture are known, the initial event in the pathogenesis of DR is a matter of debate at present. In several studies, DR was reported to be a microangiopathy. However, the scantiness of this definition is propounded by the determination of some functional impairments attributed to the effects of DM on retinal neurons before detection of microangiopathic changes.[11]

Some animal studies have demonstrated that DM causes nerve fiber impairment and results in ganglion cell apoptosis due to the impairment of retrograde axonal transport in ganglion cells.[12] In an experimental study, Hammes et al.[13] reported that DM initially caused apoptosis in retinal ganglion cells and Muller cells. The ganglion cell damage can also be a result of blood flow insufficiency associated with diabetic microangiopathy which leads to anoxia and damage of retinal nerve fiber layer.[14]

Barber et al.[15] demonstrated the neural cell death in internal plexiform, internal nuclear layer and ganglion cells in diabetic cavies and postmortem diabetic patients' eyes from the first months of disease even without DR, which confirms the triggering effect of DM on the apoptosis in neuronal cells. Observation of defects in RNFL preceding the development of ophthalmoscopically determined DR findings supports this hypothesis.[13,16-18]

Chihara et al.[17] demonstrated evident RNFL defects in DM patients similar to glaucoma by using scanning laser ophthalmoscope. No increase was detected in cup to disc ratio which helps to differentiate it from RNFL defects in normotensive glaucoma. In our study, the mean RNFL thickness was also significantly thinner compared to healthy sub-

jects, although there was no increase of cup to disc ratio.

In the study of Pengh et al.[19] the mean and superior quadrant peripapillary RNFL thickness was slightly less in diabetic patients without abnormal vascular manifestations compared to healthy subjects. Another study of Lopes et al.[9] also demonstrated significant RNFL loss with NFA-GDx in the superior segment of the retina in patients with type 1 DM without DR when compared to control group. In their study, the criteria for inclusion was type 1 DM for at least 10 years without DR to allow enough time for the development of DR. Chihara et al.[14] demonstrated that the RNFL defects in type 1 and type 2 DM patients without DR were significantly more frequent than the control group. In this study patients with DM for more than 10 years and without DR were enrolled.

In our study, we aimed to determine the difference of the RNFL thickness of type 1 DM patients with or without DR compared to control subjects and noted statistically significant RNFL thinning in type 1 DM patients with DR while there was a faint thinning of RNFL thickness in the diabetic group without DR. In accordance with our study, van Dijk et al.[20] also reported faint thinning of RNFL in patients with no or minimal DR, and Oshihari et al.[21] showed altered RNFL thicknesses at the early stage of diabetic retinopathy.

In contrast to the literature, there was no statistically significant difference in superior, nasal, inferior and temporal RNFL thicknesses in group without retinopathy compared to control group (p= 0.142, p= 0.165, p= 0.498 and p= 0.396, respectively) in our study. This difference may be a result of the shorter duration of DM in patients without DR in our study which was 60.76 ± 50.41 months. Several studies demonstrated that the RNFL thickness in the superior segment of the retina decreased more than the other regions in DM, however the statistical analysis of our results revealed no statistically significant difference in S_{max}/ I_{max} values between groups 1 and 2 (p= 0.843).[9,10,14] In this respect, RNFL loss is equal in superior and inferior quadrants in type 1 DM patients.

According to our findings, the mean RNFL thickness, superior, inferior and nasal RNFL thickness and other OCT parametric values such as S_{max}, S_{avg}, I_{max} and I_{avg} were significantly lower in group 2 as expected with the progression of retinopathy except the temporal quadrant. There was less RNFL thickness change in the temporal quadrant in group 2 and group 1 compared to other quadrants. This difference may be related to the resistance of the temporal quadrant to diabetic retinopathy which needs to be proven with further studies, evaluating the susceptibility of different retinal regions to ischemia caused by angiopathy or hyperglycemia.

Our study demonstrated a slight decrease of RNFL thickness before the development of DR and a significant RNFL thinning in type 1 DM patients with DR. These results show promise for the early detection and follow-up of diabetic retinopathy patients, before an established clinical diagnosis, by the aid of RNFL thickness follow-up.

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