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Assessment of optic disc and ganglion cell layer in diabetes mellitus type 2

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Abstract

The purpose of this study was to compare the optic disc parameters, retinal nerve fiber (RNFL), and macular ganglion cell layers between patients with diabetes mellitus (DM) type 2 and healthy controls.

In this cross-sectional study, 69 eyes of 69 diabetic patients without diabetic retinopathy and 47 eyes of 47 healthy controls were included. Optic disc parameters (i.e., rim area, disc area, cup to disc ratio, cup volume), RNFL, and macular ganglion cell-inner plexiform layers (GCL+IPL) thickness were measured by means of spectral domain optical coherence tomography.

There were not statistically significant differences between the diabetic patients and healthy controls in terms of RNFL thickness ($P=.32$), rim area ($P=.20$), disc area ($P=.16$), cup volume ($P=.12$), and average macular GCL+IPL thickness ($P=.11$). Nevertheless, binocular RNFL thickness symmetry percentage ($P=.03$), average cup to disc ratio ($P=.02$), and superior-nasal macular GCL+IPL thickness ($P=.04$) were statistically significantly different in the diabetic and control groups.

Diabetic patients without retinopathy have more binocular RNFL thickness asymmetry, higher cup to disc ratio, and thinner sectoral macular GCL+IPL when compared to healthy controls. Our results may support the statement that DM causes inner retinal neurodegenerative changes.

Abbreviations: DM = Diabetes Mellitus, FFA = Fundus Fluorescein Angiography, GCL+IPL = Macular Ganglion Cell - Inner Plexiform Layers, IOP = Intra-ocular Pressure, logMAR = Logarithm of the Minimum Angle of Resolution, RNFL = Retinal Nerve Fiber Layer, SD-OCT = Spectral Domain Optical Coherence Tomography, SPSS = Statistical Package for the Social Sciences.

Keywords: diabetes mellitus, HbA1c, macular ganglion cell layer, optic disc, retinal nerve fiber layer

1. Introduction

Diabetes mellitus (DM) has become one of the most significant public health problems in the last decades. As the prevalence of DM and life expectancy increase worldwide, diabetic complications also increase.[1] Early detection of ocular complications of DM is important for the preservation of useful visual acuity.[2] Retinopathy is the major vision-threatening ocular effect of DM. In the early stages of diabetic retinopathy, structural neurodegenerative changes such as loss of ganglion cell bodies and reduction in thickness of the inner retinal layers have been documented, besides microvascular changes.[3]

The invention of optical coherence tomography (OCT) has allowed imaging and measuring various aspects of retina and optic disc.[4] The high resolution of spectral domain OCT (SD-OCT) allows measurement of the thickness of all individual retinal layers, including retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL).[5] In addition, the SD-OCT provides data related to optic disc. Recent studies, which used SD-OCT for assessing diabetic ocular effects, have shown that DM may reduce GCL+IPL and RNFL thicknesses in the early stages of the disease.[6] Also, it was reported that DM may affect structural and biomechanical properties of the optic nerve head.[7,8]

The main potential clinical implication of the present work is that DM may affect the retinal and optic disc parameters related to glaucoma, and this condition may cause some problems in detecting glaucomatous damage in diabetic patients. Although several studies have been published related to early-onset impact of DM on RNFL thickness, macular GCL thickness, and optic disc parameters, yet it is not possible to draw definitive conclusions about the effects of DM on the inner retina. In the present study, we sought to extend the observations on the comparison of optic disc parameters, retinal nerve fiber, and macular ganglion cell layers between diabetic patients without retinopathy and healthy controls. By doing so, we tried to evaluate the early neurodegenerative effects of DM on inner retinal structures and optic disc. In addition, we evaluated the associations between HbA1c, diabetes duration, and the studied ocular parameters. Different from the previous reports, we examined binocular RNFL thickness asymmetry as a novel parameter for inner retinal damage.

2. Materials and methods

Sixty-nine participants with DM type 2 and 47 healthy controls who recruited during 2016 were included in this cross-sectional and comparative study. The present study was conducted in accordance with the ethical standards of the Declaration of

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These data have not been previously published.

The authors report no conflicts of interest

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Helsinki and approved by the local institutional review board (Pamukkale University Ethics Committee).

2.1. Study population

The participants in both the study (i.e., diabetic patients) and control groups were recruited during the same period. To prevent potential bias originated from sampling methods, all of the "consecutively referred" patients to our clinic, who fulfilled the inclusion criteria, were recruited for the study. All of the participants in the study group had been diagnosed with DM type 2. The diabetic participants showed no signs of diabetic retinopathy bilaterally. None of the subjects exhibited any ocular pathology other than low-grade age-related cataract or was taking ocular medication at the time of the study. Subjects with any history of ocular surgery, or intravitreal injection, or laser photocoagulation, or with ametropia of >2 diopters spherical equivalent, or with systemic disease such as arterial hypertension that could affect retinal and optic disc parameters were excluded. Participants who had poor-quality SD-OCT images were also excluded. Patients with diabetic major organ complications (i.e., disorders of heart, blood vessels, nerves, kidney, etc.) were excluded. The treatment for diabetic group included only diet in 3 patients, oral antidiabetic medications in 57 patients, and insulin in 9 patients.

2.2. Ocular examinations

One eye of each participant, right eyes, was included for the study. All subjects underwent an ophthalmic examination including visual acuity assessment, biomicroscopic assessment, air-puff tonometry measurement, retinal examination, and measurement with the SD-OCT (Zeiss Cirrus HD 5000 model, Carl Zeiss Meditec, Dublin, CA). The best corrected visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent for the statistical analysis. The Cirrus HD-OCT 5000 has an A scan velocity of 27000 scans/sec with a 5 μm axial resolution and a scanning depth of 2 mm. The device uses a light of 840 nm wavelength and scans an area of 6 × 6 mm for both macula and optic disc measurements. The SD-OCT was used to measure optic disc parameters, RNFL thickness, and macular GCL + IPL thickness. For optic disc measurements, disc area, rim area, cup volume, average cup to disc ratio, vertical cup to disc ratio, average RNFL thickness, RNFL thickness in the 4 quadrants (i.e., inferior, superior, nasal, and temporal), and binocular RNFL symmetry percentage were used. RNFL symmetry percentage is defined as the degree of a RNFL thickness similarity between symmetrically opposed interocular peripapillary areas. For macular measurements, average GCL + IPL thickness, minimum GCL+IPL thickness, and GCL+IPL thickness in the 6 sectors (i.e., inferior, inferior-nasal, inferior-temporal, superior, superior-nasal, superior-temporal) were used.

2.3. Statistical analysis

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, IL) was used to analyze outcomes. Any "*P*" values <.05 were accepted as statistically significant, and all data are expressed as "mean ± standard deviation". An independent samples *t* test was used to compare the studied ocular measurements between the study and control groups. When the Levene test *P* values were >.05 for the studied variables, the independent samples *t* test was used. In cases in which assumptions for parametric *t* tests were violated, Mann-Whitney *U* test was used instead. Categorical variables were compared with the χ^2 test. The Pearson correlation analysis was used to examine the relationships among HbA1c, diabetes duration, and ocular measurements. The Bonferroni correction was applied to eliminate type 1 error because of multiple comparisons.

The primary outcome of the present study was the results of comparison of inner retinal thickness values and optic disc parameters between the diabetic and healthy eyes. The secondary outcomes were the correlations of HbA1c levels and diabetes duration with the various studied ocular parameters in the diabetic eyes.

3. Results

The age range of the participants in the diabetic group was from 42 to 75 years, whereas the age range of the controls was from 42 to 71 years. Some of the demographic and clinical characteristics of the participants are shown in Table 1. The mean intraocular pressure (IOP) was 16.5 ± 3.2 mmHg in the diabetic group, whereas it was 16.6 ± 3.2 mmHg in the control group (*P* = .93).

The mean peripapillary RNFL thickness was 95.1 ± 8.0 μm in the diabetic group and 96.5 ± 6.6 μm in the control group (*P* = .32). Segmental peripapillary RNFL thickness (inferior, superior, nasal, and temporal) measurements are shown in Table 2. There were no statistically significant differences in the quadrantal thickness values between the diabetic and control groups. The percentage of binocular RNFL thickness symmetry was 83.7 ± 9.6 in the diabetic group, whereas it was 87.3 ± 7.1 in the control group (*P* = .03).

The optic disc parameters including rim area, disc area, average cup to disc ratio, vertical cup to disc ratio, and cup volume in the diabetic subjects and healthy controls are shown in Table 3. Rim area, disc area, and cup volume were similar in the diabetic and control groups, whereas average and vertical cup to disc ratios were statistically significantly higher in the diabetic eyes. When the Bonferroni correction (α/n; 0.05/5) was made, the only statistically significant result was the high vertical cup-to-disc ratio in the diabetic eyes.

The mean "average" GCL + IPL thickness was 82.2 ± 6.1 μm in the diabetic eyes and 83.9 ± 4.7 μm in the controls (*P* = .11). The mean "minimum" GCL + IPL thickness was 78.5 ± 7.2 μm in the diabetic group and 81.0 ± 5.0 μm in the control group (*P* = .04). The sectoral macular GCL + IPL thickness values in the diabetic and control groups are demonstrated in Table 4. The sectoral thickness values of GCL + IPL in the diabetic eyes were thinner than that of the controls, but this difference was statistically significant only in the superior-nasal area.

The mean HbA1c value was 7.7 ± 1.9 (range: 4.9–12.5) in the diabetic group. The mean DM duration was 7.5 ± 5.2 (range: 1–20) years. The correlations of HbA1c levels and diabetes

Table 1

Some of the characteristics of the participants are shown.

	Diabetic group	Control group	*P*
Mean age, y	56.8 ± 8.8	56.2 ± 6.4	.71
Sex (M/F)	29 M, 40 F	20 M, 27 F	.96
SE, diopters	0.17 ± 0.79	0.41 ± 0.74	.11
Visual acuity (log*MAR*)	0.011 ± 0.032	0.004 ± 0.020	.17

F = female, logMAR = logarithm of the minimum angle of resolution, M = male, SE = spherical equivalent of refractive error.

Table 2

Segmental peripapillary RNFL thickness (inferior, superior, nasal, and temporal) values in the diabetic and control groups are demonstrated.

	Diabetic group	Control group	P
Inferior quadrant, μm	125.6±15.4	127.8±11.5	.40
Superior quadrant, μm	115.8±13.5	119.7±14.7	.14
Nasal quadrant, μm	73.0±10.1	73.5±9.1	.79
Temporal quadrant, μm	66.1±8.9	64.4±9.3	.32

RNFL = retinal nerve fiber layer.

duration with the various studied ocular parameters in the diabetic eyes are shown in Table 5. There were no significant correlations between the HbA1c levels and the IOP, RNFL, GCL +IPL, and optic disc parameters. Diabetes duration was statistically significantly correlated only with binocular RNFL symmetry percentage.

4. Discussion

The outcomes of the present study show that diabetic patients without any signs of ocular involvement have more binocular RNFL thickness asymmetry, higher cup to disc ratio and thinner macular GCL+IPL when compared to healthy controls. Since early detection of diabetic ocular complications is utmost important to maintain a useful vision, the thinning of the inner retinal layers such as RNFL, GCL, and IPL may indicate initial damage of DM on the posterior pole before the appearance of obvious retinal findings.

In the present study, higher percentage of binocular RNFL asymmetry found in diabetic eyes may support the emergence of early neuronal alterations in DM. Also, it was reported that an interocular difference of the mean peripapillary RNFL thickness might indicate an early glaucomatous damage.[9] According to us, binocular RNFL symmetry percentage may help the clinicians to assess the effects of diabetes duration on the inner retina, since we found that diabetes duration was correlated with the binocular RNFL thickness asymmetry. As a novel contribution to the literature, this study may show the relation between RNFL thickness symmetry and DM.

In a recent study, it was reported that GCL+IPL and RNFL thickness values were markedly reduced in diabetic eyes without retinopathy and the authors concluded that neuroretinal alterations may precede microvascular abnormalities in DM.[6] Takis et al[10] showed that the mean inferior sectoral RNFL thickness was significantly lower in diabetic patients with no or mild retinopathy compared to that of healthy eyes. There is an increasing evidence that DM can cause alterations in neural retina, including loss of ganglion cells.[11–13] In our study, the

Table 3

Optic disc parameters taken by SD-OCT in the diabetic and control groups are shown.

	Diabetic group	Control group	P
Rim area, mm^2	1.42±0.23	1.49±0.29	.20
Disc area. mm^2	1.94±0.32	1.86±0.25	.16
c/d Average	0.48±0.16	0.39±0.18	.02
c/d Vertical	0.46±0.15	0.38±0.17	.01
Cup volume, mm^3	0.13±0.12	0.09±0.11	.12

c/d = cup to disc ratio, SD-OCT = spectral domain optical coherence tomography.

Table 4

Sectoral macular GCL+IPL thickness (inferior, inferior-nasal, inferior-temporal, superior, superior-nasal, and superior-temporal) values in the diabetic and control groups are demonstrated.

	Diabetic group	Control group	P
Inferior, μm	81.4±6.6	83.0±4.8	.17
Inferior-nasal, μm	82.3±7.0	84.3±6.0	.11
Inferior-temporal, μm	82.9±6.4	84.1±4.6	.27
Superior, μm	82.8±6.8	84.8±5.2	.09
Superior-nasal, μm	82.7±7.4	85.3±5.7	.04
Superior-temporal, μm	81.0±6.3	81.7±4.9	.52

GCL = ganglion cell layer, IPL = inner plexiform layer.

macular GCL+IPL thickness was reduced in several sectors in the diabetic eyes and those outcomes were concordant with the outcomes of the previous studies.

Optic disc may be affected in DM in several aspects.[7,14] Terai et al[7] reported that DM affected biomechanical properties of optic disc in an animal model. Elgin et al[15] demonstrated that non-glaucomatous eyes of children with type 1 DM and healthy controls have similar topographic optic nerve head findings. In a large population-based study, it was reported that neuroretinal rim area is not associated with a known diagnosis of DM.[16] In this study, we have found that average and vertical c/d ratios were higher in diabetic eyes without retinopathy compared to the controls. Although it may be incidental, this outcome may be occurred due to the larger disc area and smaller rim area measured in the diabetic group. Those findings may indicate a relative predisposition of diabetic eyes to glaucomatous optic disc damage in long-term follow-up, but in contrary to that statement, average RNFL thickness was found to be similar in both the diabetic and control eyes.

In our study, HbA1c and DM duration were not associated with any of the studied ocular parameters, except for a moderate correlation between binocular RNFL symmetry percentage and DM duration. It was reported that macular thickness is inversely correlated with longer duration of diabetes and HbA1c levels.[17] However, Srinivasan et al[18] reported that HbA1c and diabetes duration were not related with retinal tissue thickness. Sugimoto et al[19] found that glycemic control (i.e., HbA1c levels) affects RNFL within 4 months. Sahin et al[20] showed that there is a mild negative correlation between HbA1c and average RNFL thickness, and concluded that thinning of RNFL might be

Table 5

The correlations of HbA1c levels and diabetes duration with the various studied ocular parameters in the diabetic eyes are shown.

	HbA1c		Diabetes duration	
	r	P	R	P
IOP	0.003	0.98	0.13	.31
RNFL average	0.03	0.79	0.04	.75
RNFL symmetry	0.10	0.42	0.25	.04
Rim area	−0.06	0.63	−0.12	.32
Disc area	0.06	0.61	0.05	.69
c/d Average	0.10	0.42	0.17	.17
c/d Vertical	0.17	0.18	0.15	.21
Cup volume	0.09	0.46	0.02	.86
GCL+IPL average	0.03	0.82	−0.13	.28
GCL+IPL minimum	0.001	0.99	−0.15	.23

c/d = cup to disc ratio, GCL = ganglion cell layer, IOP = intraocular pressure, IPL = inner plexiform layer, RNFL = retinal nerve fiber layer.

related with increased rates of atherosclerosis in patients with type 2 DM.

One of the main clinical implications of the present study is the finding that the diabetic eyes without apparent retinopathy may have subtle inner retinal pathology. It may be suggested that clinicians should use more sophisticated ocular diagnostic tools to detect early diabetic retinal abnormalities, in addition to performing standard slit-lamp biomicroscopy examination with a 78-diopter or 90-diopter lens. During routine clinical ophthalmology practice, it would be helpful to remember that DM may cause inner retinal and optic disc alterations similar to glaucoma.

Our study has several limitations. First, the present study did not include patients with diabetic retinopathy. Because OCT measurement quality might be low in advanced diabetic retinopathy because of exudates and hemorrhages. Second, we did not have fundus fluorescein angiography (FFA), which might show the earliest retinopathy findings that could not be noticed by routine retinal examination. But there were no clear clinical indications for FFA in our cases. Lastly, it would be nice if we had OCT angiography examinations. In the present study, we used Zeiss Cirrus HD-OCT 5000. Brautaset et al[21] reported that the repeatability of this device is high in both macula and optic disc measurements because of its automatic tracking function. According to us, one of the major strengths of the present study was the demonstration of higher binocular RNFL thickness asymmetry in diabetic eyes compared to healthy eyes, which might indicate early inner retinal neurodegenerative process in DM without retinopathy.

In conclusion, diabetic eyes and healthy controls have similar RNFL thickness, rim area, disc area, cup volume, and average GCL + IPL thickness. Nevertheless, diabetic eyes have higher percentage of binocular RNFL asymmetry, higher average and vertical c/d ratios, thinner minimum and superonasal GCL + IPL thickness. As the examination techniques used in the present study are specific to glaucoma diagnosis, our findings may indicate a relative predisposition of diabetic eyes to glaucomatous retinal damage. In addition, we should speculate that DM may make difficult to detect pure glaucomatous posterior pole damage. In further longitudinal studies, the study group may be extended to cover diabetic patients in various stages of diabetic retinopathy.

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