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RESEARCH ARTICLE

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Evaluation of optical coherence tomography angiography and pattern and flash electroretinography in diabetes mellitus without retinopathy

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ABSTRACT

Purpose: To evaluate the findings and the correlation of optical coherence tomography angiography and pattern and flash electroretinography in diabetes mellitus without retinopathy.

Methods: Seventy-six eyes of 38 diabetic patients and age- and gender-matched control subjects were included in the study. The foveal avascular zone (FAZ), whole, foveal, parafoveal and perifoveal vascular densities of the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillary plexus (CCP) layers were analyzed using optical coherence tomography angiography (OCTA). The amplitudes and implicit times of P50 and N95 waves of the pattern ERG (pERG) and the amplitudes and implicit times of the scotopic and photopic b-waves and oscillatory potentials (OP) of the flash ERG (fERG) tests were evaluated using the Metrovision brand monpack model device.

Results: The mean age of the patients was 59.7±7.9 [range 43–79] years. Eighteen (47%) of the patients were female and 20 (53%) were male. The mean duration of diabetes was 7.45±6.2 [range 1–20] years. No significant difference in FAZ area was found between study subjects and controls. Vascular density (VD) values of the superficial capillary plexus (SCP) layer were significantly lower (whole VD, 44.7±3.3 vs. 46.6±3.2%, $p=0.01$, foveal VD 16.8±6.4 vs. 24.9±6.1%, $p<0.01$, parafoveal VD 45.6±4.5 vs. 47.1±4.4%, $p=0.27$ and perifoveal VD 45.5±3.3 vs. 47.3±3.1%, $p=0.01$, respectively) in the diabetic group except the parafoveal area. VD measurements in deep and choriocapillary plexuses did not significantly differ between the groups ($p>0.05$). ERG tests revealed significantly lower scotopic b-wave amplitudes (130.2±39.3 µV vs.163.3±47.8 µV, $p<0.01$) and photopic b-wave amplitudes (83.2±20.7 µV vs. 99.6±29.4 µV, $p<0.01$) in the diabetic patients. The implicit time of the photopic responses was significantly prolonged (28.9±1.3 ms vs. 27.8±2.1 ms, $p=0.01$) in the patients. Oscillatory potentials in all components consisting of O1 to O4 and the sum of the OP potentials were lower in the diabetic group than the control subjects ($p<0.001$). The P50 and N95 amplitudes and implicit times were comparable between the groups ($p>0.05$). Correlation analysis showed a positive correlation between N95 amplitudes in pERG and the superficial vessel densities in OCTA ($r=0.26$, $p=0.04$). A negative correlation was found between photopic implicit times in fERG and the choriocapillary vessel densities (r=-0.27, $p=0.03$).

Conclusion: OCTA revealed decreased superficial vascular densities with the onset of the metabolic process of diabetes mellitus. As a result of these structural changes, lower scotopic and photopic amplitudes, decreased OP amplitudes, and prolonged implicit times in flash ERG were obtained.

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Diabetes mellitus; retinopathy; optical coherence tomography angiography; pattern electroretinography; flash electroretinography

Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes mellitus and the leading cause of preventable blindness in the working population. DR can be diagnosed by the microaneurysms and retinal hemorrhages seen on ophthalmoscopy and color fundus photography. Nonetheless, microvascular damage due to the reduction of retinal perfusion is known to begin before the findings are detected on clinical examination [1].

The increased clinical use of optical coherence tomography angiography (OCTA), which is a current noninvasive angiographic technique, has revealed important pathophysiological findings such as decreased superficial and deep parafoveal vascular

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densities in diabetes mellitus without clinically apparent retinopathy [2]. Additionally, an increase in FAZ area was detected in diabetic subjects compared to controls, suggesting subclinical macular ischemia [3].

Pattern and flash ERGs are both non-invasive and sensitive methods for detecting early pathological changes. Flash ERG assesses the electrophysiological response of the entire retina to a light stimulus. Oscillatory potentials (OPs) represent interactions of the inner retinal cells and amacrine cells, and are related to ischemic retinal conditions, proposing early functional changes before the appearance of vasculopathy [4,5]. Studies have shown prolongation of the implicit time or a reduction of the oscillatory potential amplitudes of the full-field ERGs, which demonstrate abnormal function of the inner retinal neurons, in diabetic patients with no clinically detectable retinopathy [6,7]. Pattern ERG is also an objective method showing both retinal neuron and optic nerve functions in diabetic patients [8]. Some studies have depicted significantly reduced P50 and N95 amplitudes and delayed implicit times in diabetic patients with no retinopathy, indicating the impairment of macular cone cells and retinal ganglion cells [9,10].

Few studies have investigated the combined results of ERG and OCTA assessments in diabetic patients without clinically apparent diabetic retinopathy. Pandurangan et al. have reported a significant decrease in functional parameters measured by fERG, especially in the photopic negative response, while the OCTA findings were normal in diabetic patients without retinopathy [11]. Zeng et al. have described a decrease in vascular parameters in SCP and delayed implicit time with decreased amplitudes in ERG parameters in diabetes with no retinopathy [12].

In this study, we aimed to evaluate the findings of the optical coherence tomography angiography and pattern and flash electroretinography in diabetes mellitus without retinopathy.

Methods

A total of 38 diabetic patients without retinopathy and 38 age- and gender-matched control subjects were enrolled in the study, which was approved by the Institutional Review Board of Ankara City Hospital and complied with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the participants.

Patients who had been diagnosed with type 2 diabetes mellitus for more than one year without any signs of diabetic retinopathy were analyzed. Examinations comprised the measurement of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated fundoscopy, optic coherence tomography angiography (OCTA) imaging, pattern and flash-ERG tests. All patients and control subjects had a BCVA of 20/20. Exclusion criteria included the presence of any retinal vascular disease, glaucoma, macular degeneration, optic neuritis, previous laser treatment and additional systemic or neurological diseases. High myopia in addition to other refractive errors more than 3 diopters were also excluded.

For OCTA images, the AngioVue OCTA (RTVue, Optovue, CA, USA) system was used in a 6×6 mm scanning area with 70,000 A-scans per second. The instrument uses a scanning light centered at 840 nm with a bandwidth of 45 nm and provides 5 µm axially tissue resolution [13]. The superficial, deep and choriocapillary vascular layers were generated automatically by the software. The superficial capillary plexus (SCP) layer was defined as a slab extending from 3 to 15 microns from the inner limiting membrane. The deep capillary plexus (DCP) layer was defined as a slab extending from 15 to 70 microns below the inner limiting membrane and a slab extending from 30 to 60 microns below the retinal pigment epithelium was the reference for the choriocapillary plexus (CCP) layer. Low-quality images with a signal strength index < 50 were excluded. Vessel densities were measured as the ratio of the vessel pixels to the total number of pixels as a percentage. The foveal avascular zone (FAZ) was measured qualitatively after automated detection in mm^2.

In accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards, the pattern (pERG) and flash ERG (fERG) tests were performed using the Metrovision brand monpack model device [14]. For pERG, corneal recording test electrodes were placed on the tested eyes. The reference and ground electrodes were placed in the outer canthus and the forehead. Stimulation was supplied from a television screen in the shape of a chessboard. For the fERG test, performed after pupillary dilation, dark-adapted (DA) ERG, light-adapted (LA) ERG, and LA flicker ERG were done. Hawlina–Konec loop electrodes were used. For dark adaptation, patients were kept in total darkness for 30 min. The DA ERGs included responses to flash strengths (in photopic units; phot) of 0.01, 1.0, 3 and 10 phot cd·s·m^{-2} (DA 0.01; DA 1.0; DA 3; DA 10). For light adaptation, patients were given 15 min to adapt to the light. The LA ERGs were to a flash strength of 3 phot cd·s·m^{-2}, superimposed on a light-adapting background (luminance 30 cd·m^{-2}) as single flashes (LA 3 ERG) and at a frequency close to 30 Hz (LA flicker 30 Hz ERG). Rod response b-wave

amplitudes (μV) and cone response b-wave amplitudes (μV), and flicker responses (μV) were compared [10].

Statistical analysis

Statistical analyses were performed with the SPSS 18.0 software (SPSS, Inc. Chicago, IL, USA). Demographic data were presented as percentages and clinical data as means and standard deviations. The normality of the data was evaluated with the Shapiro-Wilk test. The Mann-Whitney U-test was used for the comparisons between groups. Spearman correlation coefficients were calculated to assess correlations between whole, foveal, perifoveal and parafoveal vessel densities and ERG parameters. $p<0.05$ was considered statistically significant.

Results

A total of 38 (18 female, 20 male) patients and 38 (16 female, 22 male) control subjects were enrolled. The mean age was 59.7 ± 7.9 [range 43–79] years and 58.2 ± 6.4 [range 43–68] years in the diabetic and control groups, respectively. No difference was detected between the groups in terms of age and gender ($p=0.37$, $p=0.64$). The mean duration of diabetes mellitus was 7.45 ± 6.2 [range 1–20] years. The BCVA was 20/20 in all patients in both groups. Slit-lamp biomicroscopy findings revealed no evidence of cataract or other anterior segment abnormality. Dilated fundoscopy did not show any retinal vascular abnormality. The participants' demographic information is listed in Table 1.

The FAZ area of the diabetic and control subjects was 0.282 ± 0.10 mm^2 and 0.287 ± 0.11 mm^2, respectively. There was no significant difference between the groups ($p=0.14$). Vascular density (VD) values of the superficial capillary plexus (SCP) layer except the parafoveal area were significantly lower in the diabetic group than in the control subjects ($p<0.05$). However, VD measurements in deep and choriocapillary plexuses did not significantly differ between the groups ($p>0.05$) (Table 2).

In electrophysiological studies, the PERG test results revealed comparable amplitudes and implicit times of the P50 and N95 waves between the groups ($p>0.05$). The FERG test showed significantly lower scotopic amplitudes with a mean value of 130.2 ± 39.3 μV and photopic amplitudes with a mean value of 83.2 ± 20.7 μV in the diabetic patients ($p<0.01$). The mean implicit time of the rod responses was comparable between the groups (43.9 ± 3.1 ms vs. 43.4 ± 3.7 ms, $p=0.38$). However, the mean implicit time of the cone responses was statistically significantly prolonged in these subjects (28.9 ± 1.3 ms vs. 27.8 ± 2.1 ms, $p=0.01$). Oscillatory potentials of all components (O1–O4, 15.5 ± 5.2, 33.4 ± 12.4, 33.4 ± 13.7, 27.4 ± 12.0 μV, respectively) and the sum of OP amplitudes (85.5 ± 36.5 μV) were significantly lower than the control subjects ($p<0.001$) in the diabetic group. However, implicit times of the OPs were comparable between the groups (Table 3; Figure 1).

Evaluating the correlation between the whole vessel densities in the capillary layers and ERG parameters revealed a positive correlation between the N95 amplitudes and superficial vessel density ($r=0.26$, $p=0.04$). Moreover, the photopic implicit time values were negatively correlated with the choriocapillary vessel densities (r= −0.27, $p=0.03$). There was no correlation between the sum of OP amplitudes and vessel densities in the capillary layers. The correlations between electrophysiological parameters including all OP components and foveal, parafoveal and perifoveal areas in SCP, DCP and CC layers showed no statistical significance between the diabetic and control groups (Table 4).

Discussion

Optical coherence tomography angiography (OCTA) has been widely investigated and several studies have

Table 1. Demographic data of the study groups.

Characteristics	Diabetic group	Control group
N. of participants	38	38
Gender (female/male, %)	18/20 (47/53)	16/22 (42/58)
Mean age ± SD, years	59.7 ± 7.9	58.2 ± 6.4
Diabetes duration ± SD, years	7.45 ± 6.2	NA

N: number, SD: standard deviation, NA: not available.

Table 2. Comparison of optical coherence tomography angiography parameters between the groups.

Parameters	Diabetic group	Control group	*p**
Foveal avascular zone (mm^2)	0.282 ± 0.10	0.287 ± 0.11	0.14
SCP (VD, %)			
Whole	44.7 ± 3.3	46.6 ± 3.2	*0.01**
Foveal	16.8 ± 6.4	24.9 ± 6.1	*<0.01**
Parafoveal	45.6 ± 4.5	47.1 ± 4.4	0.27
Perifoveal	45.5 ± 3.3	47.3 ± 3.1	*0.01**
DCP (VD, %)			
Whole	44.0 ± 5.1	45.5 ± 4.9	0.52
Foveal	33.8 ± 6.9	35.7 ± 6.8	0.09
Parafoveal	50.6 ± 4.2	51.6 ± 4.6	0.96
Perifoveal	45.7 ± 5.5	46.2 ± 5.6	0.56
CCP (VD, %)			
Whole	66.4 ± 7.1	67.8 ± 3.4	0.17
Foveal	65.1 ± 8.6	60.9 ± 7.6	0.55
Parafoveal	65.6 ± 6.4	66.4 ± 3.8	0.37
Perifoveal	67.4 ± 6.7	68.6 ± 3.6	0.15

*p value of the Mann-Whitney U-test.
SCP: superficial capillary plexus, DCP: deep capillary plexus, CCP: choriocapillary plexus, VD: vascular density.

revealed a decrease in vascular densities in diabetic subjects [2,15–17]. The findings of the current study have revealed lower SCP vessel densities. Endothelial cell damage and pericyte loss in the capillaries due to retinal ischemia may result in deterioration of the superficial vascular layers. Ong et al. [16] have also described a downward trend in the SCP (46.38 ± 4.93% in the healthy group vs. 45.76 ± 4.77% in the diabetic group with no retinopathy) with increased severity of retinopathy. Zeng et al. indicated significantly decreased parafoveal and perifoveal VDs in both superficial and deep capillary layers (49.97 ± 4.45 and 48.12 ± 4.01% in the SCP, 52.70 ± 4.51 and 48.62 ± 6.39% in the DCP) in the diabetic group and a correlation between delayed implicit times in FERG and the parafoveal VD decrease in the SCP [12].

Table 3. Comparison of electrophysiological test results between the groups.

Electrophysiological tests	Diabetic group	Control group	*p**
Pattern ERG			
P50 amplitude	4.69 ± 2.49	4.72 ± 3.25	0.95
		51.0 ± 1.3	
Implicit time	52.5 ± 5.8	−5.30 ± 4.46	0.36
N95 amplitude	−5.18 ± 3.03	88.6 ± 17.6	0.47
Implicit time	91.9 ± 16.4		0.24
Scotopic b-wave			
Amplitude	130.2 ± 39.3	163.3 ± 47.8	*<0.01**
Implicit time	43.9 ± 3.1	43.4 ± 3.7	0.38
Photopic b-wave			
Amplitude	83.2 ± 20.7	99.6 ± 29.4	*<0.01**
		27.8 ± 2.1	
Implicit time	28.9 ± 1.3		*0.01**
OP amplitudes			
OP1 amplitude	15.5 ± 5.2	21.2 ± 7.1	*<0.001**
OP1 implicit time	19.5 ± 1.5	19.3 ± 2.2	0.56
OP2 amplitude	33.4 ± 12.4	49.6 ± 16.4	*<0.001**
OP2 implicit time	22.9 ± 1.7	22.6 ± 1.7	0.28
OP3 amplitude	33.4 ± 13.7	50.8 ± 16.6	*<0.001**
OP3 implicit time	26.3 ± 3.1	25.8 ± 2.0	0.24
OP4 amplitude	27.4 ± 12.0	45.7 ± 16.4	*<0.001**
OP4 implicit time	29.5 ± 3.1	28.7 ± 1.8	0.06
Sum of OP amplitudes	85.5 ± 36.5	139.6 ± 49.4	*<0.001**

*p value of the Mann-Whitney U-test.
Amplitudes are in microvolts (μV) and implicit times are in milliseconds.

Early studies of the cellular origins in pERG highlighted the P50 peak because of its similarity to the b response on the full-field electroretinogram. Mafei and Fiorentini demonstrated that the pERG amplitude was completely lost with the retrograde damage to the retinal ganglion cells. Additional human and experimental studies have shown that pERG reflects ganglion cell function, but also has a contribution from the distal retina [18]. On the other hand, there are controversial data regarding the abnormalities and importance of pERG in diabetes. Deák et al. have depicted significantly reduced P50 and N95 amplitudes (5.53 ± 2.54 μV) and delayed implicit times (55.81 ± 4.65 ms and 100.1 ± 8.36 ms) in diabetic patients with no retinopathy [10]. However, Park et al. have reported nonsignificant abnormalities in pERG (9.77 ± 2.15 μV), photopic negative response (37.29 ± 11.25 μV) in fERG and post-illumination pupil response (0.37 ± 0.11 μV) in diabetic subjects who had no clinically apparent diabetic retinopathy [19]. Our results have also shown minimally reduced P50 and N95 amplitudes and prolonged implicit times in the diabetic group, without statistical significance. Arden et al. have emphasized that pERG is a sensitive indicator of maculopathy in diabetes, and the mean pERG values of 4.8 ± 9 μV(3.7–6.2) are reduced with the presence of fundoscopic and angiographic areas of capillary nonperfusion despite the lack of any visual symptoms [20]. Another study has also indicated reduced pERG amplitudes with a mean value of 0.40 μV compared to the

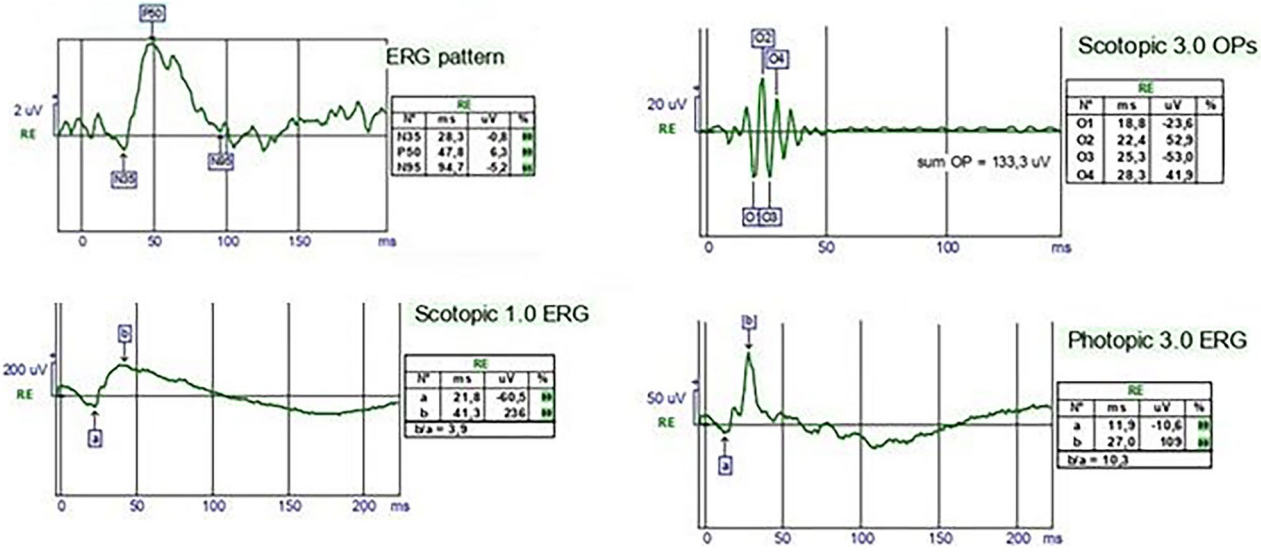

Figure 1. Representative ERGs in the diabetic without retinopathy.

Table 4. Spearman's correlation coefficients of functional and structural parameters in the diabetic and control groups.

	Superficial VD		Deep VD		CCP VD	
Parameters	Diabetic	control	Diabetic	control	Diabetic	control
Pattern ERG						
P50 amplitude	−0.06, 0.61	0.48, 0.47	0.18, 0.17	−0.04, 0.70	−0.03, 0.83	0.08, 0.50
Implicit time	0.10, 0.43	0.06, 0.61	0.09, 0.45	0.12, 0.28	0.12, 0.37	−0.16, 0.17
N95 amplitude	***0.26, 0.04****	−0.09, 0.42	0.02, 0.88	0.07, 0.52	−0.03, 0.82	−0.07, 0.51
Implicit time	−0.23, 0.07	0.18, 0.11	−0.05, 0.72	−0.05, 0.68	−0.24, 0.06	−0.14, 0.21
Scotopic b-wave						
Amplitude	0.08, 0.51	0.06, 0.59	−0.05, 0.68	0.15, 0.20	0.11, 0.40	−0.28, 0.12
Implicit time	0.12, 0.32	−0.14, 0.25	0.14, 0.26	0.08, 0.46	0.08, 0.52	−0.11, 0.35
Photopic b-wave						
Amplitude	−0.179, 0.151	0.10, 0.39	−0.002, 0.98	0.15, 0.18	0.151, 0.225	−0.23, 0.06
Implicit time	−0.168, 0.179	−0.03, 0.81	−0.15, 0.23	0.09, 0.43	***−0.27, 0.03****	−0.07, 0.52
Sum of OP						
Amplitude	0.02, 0.89	0.17, 0.12	0.07, 0.52	0.11, 0.33	−0.04, 0.75	−0.04, 0.71

VD: vascular densities of the whole capillary plexus.
OP: Oscillatory potential, *Factors with statistically significance.

controls in insulin-dependent diabetics with no clinical evidence of retinopathy [21]. Yet another study has demonstrated lower P50-N95 component amplitudes of pERG parameters with a mean value of 3.19 ± 1.60 µV in diabetic patients with no clinically evident retinopathy. This last study demonstrated significant alterations in pERG parameters associated with the degree of the DR severity in type 2 diabetes mellitus [22].

Considering the higher metabolic demand and elevated oxidative stress of the diabetic retina, reduced b-wave amplitudes can be expected in the fERG. Kim et al. have also described abnormal amplitudes and implicit times in the rod-derived ERG responses (149.62 ± 51.48 µV and 105.59 ± 10.44 ms) in the group without diabetic retinopathy, but the alteration in the cone-derived ERG responses was not significant. They pointed out a tendency for decreased values, in accordance with DR severity, including the scotopic b-wave, combined b-wave, photopic b-wave, and oscillatory potentials [23]. Our results showed similarly reduced scotopic ERG amplitudes and prolonged implicit times in the diabetic group but the photopic response amplitudes and implicit times were also lower. Furthermore, a recent study emphasized a prolongation of the combined photoreceptor and bipolar cell responses in the scotopic ERG in the diabetes mellitus without retinopathy and nonproliferative diabetic retinopathy groups [7].

Our study revealed significantly decreased OP values in terms of all the components and the sum OP values in the diabetic group. Similarly, Gualtieri et al. tested 34 diabetic patients and reported that the inner retinal component data obtained from oscillatory potentials were more significantly affected than those from the outer retinal components and were associated with confounded color discrimination without retinopathy. They indicated that abnormal responses were more prevalent in O1 OP, with a percentage of 85% [6]. Luu et al. also described decreased OP amplitudes from OP1 to OP4 (15.42 ± 4.06, 25.12 ± 7.37, 12.09 ± 5.32, 7.04 ± 3.08 µV) and a significantly lower implicit time of OP2 (25.64 ± 0.81 ms) in the group without diabetic retinopathy [24]. Coupland et al. have also stated that the OP amplitudes (OP1:1.2 ± 1.20, OP2: 5.1 ± 1.45, OP3:3.1 ± 0.9, OP4:2.9 ± 0.99 µV) were found to be significantly diminished in diabetic patients with no evidence of diabetic retinopathy accompanying the normal pERG values (P-Q wave amplitude as 2.9 ± 1.9 µV vs. 3.2 ± 1.8 µV and Q-R wave amplitude as 6.8 ± 2.5 µV vs. 6.8 ± 2.0 µV). Therefore, the study reported that OP measures were more sensitive than pERG measures in identifying abnormal electroretinal function in diabetic patients with no photographic retinopathy [25].

The correlation analysis showed a positive correlation between the N95 amplitudes in pERG and superficial vessel densities in OCTA images and a negative correlation between the photopic implicit times in fERG and the choriocapillary vessel densities. Our findings suggest that the decrease in superficial vascular density is associated with the pERG parameters, resulting in decreased N95 amplitudes in electrophysiological studies. When the relationship between photoreceptor integrity and retinal perfusion is considered, it may also be hypothesized that the decrease in choroidal perfusion results in the deterioration of cone retinal functions. Therefore, the microvascular impairment could be promoting the retinal cell damage detected by electrophysiological studies.

According to the study of Kim et al. a positive correlation was identified between the scotopic and combined b-wave amplitudes and vessel densities of the superficial plexus. The study also denoted a negative correlation between the implicit times and superficial VDs in the scotopic and combined response b-waves [23]. A recent study has also emphasized the correlation

of inner retinal function with vascular responses to flicker light. These results of retinal functional tests suggest neuronal impairment in diabetic patients [9]. Ebihara et al. emphasized that the OP amplitudes were significantly smaller with a decrease in the VDs of the SCP in diabetic eyes. They also found that the implicit times of the OP1–OP3 were significantly prolonged with a decrease in the VDs of the DCP [26]. In our study, despite the reduced OP amplitudes in diabetic patients without retinopathy, a significant association was not present between the OP values and vascular parameters. In the light of these results, ERG provides sensitive information in identifying early changes preceding the clinical manifestations of diabetic retinopathy.

Our finding of a prolonged photopic implicit time with decreased choriocapillary vascular density could indicate that the cell functions are impaired due to the decrease of retinal perfusion prior to clinically apparent vascular abnormalities. Deng et al. also described that the choriocapillary flow density ($1.99 \pm 0.1\,mm^{2)}$ was decreased in patients with diabetes and correlated with ERG parameters [27]. These results may be useful in predicting the use of retinal neural functional tests to correlate their results with neurovascular function.

Limitations of this study include the small sample size and the lack of metabolic control in the diabetic patients. In addition, we evaluated newly diagnosed diabetic patients presenting to the clinic. The included patient group had a rather large span of diabetes duration, and the electrophysiological tests could have been affected differently.

In conclusion, vascular and structural changes detected by OCTA and ERG tests demonstrate that retinal cell functions are affected in the early period without any retinal finding in diabetic patients. Earlier recognition and identification of microvascular and neural changes are important in terms of determining the severity of the disease and preventing vision loss. Future studies promise to develop methods for the appropriate management for patients at risk for diabetic retinopathy.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara City Hospital (15.06.2022/E1-21-2211).

Authors contributions

BPG, MH: designed the study; BPG: collected the data; BPG, MH: analysis and interpretation of data; BPG, MH: drafting the manuscript; BPG, MH: revising the work critically for important intellectual content. All authors approved the final version of manuscript.

Disvclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [BPG], upon reasonable request.

References

[1] Barot M, Gokulgandhi MR, Patel S, et al. Microvascular complications and diabetic retinopathy: recent advances and future implications. Future Med Chem. 2013;5(3):301–314. doi: 10.4155/fmc.12.206.

[2] Cao D, Yang D, Huang Z, et al. Optical coherence tomography angiography discerns preclinical diabetic retinopathy in eyes of patients with type 2 diabetes without clinical diabetic retinopathy. Acta Diabetol. 2018;55(5):469–477. doi: 10.1007/s00592-018-1115-1.

[3] Yasin Alibhai A, Moult EM, Shahzad R, et al. Quantifying microvascular changes using OCT angiography in diabetic eyes without clinical evidence of retinopathy. Ophthalmol Retina. 2018;2(5):418–427. doi: 10.1016/j.oret.2017.09.011.

[4] Hamurcu M, Ekinci C, Koca S, et al. Evaluation of amblyopic eyes with optical coherence tomography angiography and electrophysiological tests. Indian J Ophthalmol. 2021;69(1):105–110. doi: 10.4103/ijo.IJO_2319_19.

[5] Safi H, Safi S, Hafezi-Moghadam A, et al. Early detection of diabetic retinopathy. Surv Ophthalmol. 2018;63(5):601–608. doi: 10.1016/j.survophthal.2018.04.003.

[6] Gualtieri M, Feitosa-Santana C, Lago M, et al. Early visual changes in diabetic patients with no retinopathy measured by color discrimination and electroretinography. Psychol Neurosci. 2013;6(2):227–234. doi: 10.3922/j.psns.2013.2.11.

[7] Ba-Ali S, Larsen M, Andersen HU, et al. Full-field and multifocal electroretinogram in non-diabetic controls and diabetics with and without retinopathy. Acta Ophthalmol. 2022;100(8):e1719–e28. doi: 10.1111/aos.15184.

[8] McAnany JJ, Persidina OS, Park JC. Clinical electroretinography in diabetic retinopathy: a review. Surv

Ophthalmol. 2022;67(3):712–722. doi: 10.1016/j.survophthal.2021.08.011.
[9] Lecleire-Collet A, Audo I, Aout M, et al. Evaluation of retinal function and flicker light-induced retinal vascular response in normotensive patients with diabetes without retinopathy. Invest Ophthalmol Vis Sci. 2011; 52(6):2861–2867. doi: 10.1167/iovs.10-5960.
[10] Deák K, Fejes I, Janáky M, et al. Further evidence for the utility of electrophysiological methods for the detection of subclinical stage retinal and optic nerve involvement in diabetes. Med Princ Pract. 2016;25(3): 282–285. doi: 10.1159/000442163.
[11] Pandurangan K, Sachidanandam R, Sen P. Structural and functional changes among diabetics with no diabetic retinopathy and mild non-proliferative diabetic retinopathy using swept-source optical coherence tomography angiography and photopic negative response. Doc Ophthalmol. 2022;145(2):113–125. doi: 10.1007/s10633-022-09891-x.
[12] Zeng Y, Cao D, Yu H, et al. Early retinal neurovascular impairment in patients with diabetes without clinically detectable retinopathy. Br J Ophthalmol. 2019; 103(12):1747–1752. doi: 10.1136/bjophthalmol-2018-313582.
[13] Kaizu Y, Nakao S, Arima M, et al. Flow density in optical coherence tomography angiography is useful for retinopathy diagnosis in diabetic patients. Sci Rep. 2019; 9(1):8668. doi: 10.1038/s41598-019-45194-z.
[14] Robson AG, Frishman LJ, Grigg J, et al. ISCEV standard for full-field clinical electroretinography (2022 update). Doc Ophthalmol. 2022;144(3):165–177. doi: 10.1007/s10633-022-09872-0.
[15] Park YG, Kim M, Roh YJ. Evaluation of foveal and parafoveal microvascular changes using optical coherence tomography angiography in type 2 diabetes patients without clinical diabetic retinopathy in South Korea. J Diabetes Res. 2020;2020:6210865–6210867. doi: 10.1155/2020/6210865.
[16] Ong JX, Kwan CC, Cicinelli MV, et al. Superficial capillary perfusion on optical coherence tomography angiography differentiates moderate and severe nonproliferative diabetic retinopathy. PLoS One. 2020; 15(10):e0240064. doi: 10.1371/journal.pone.0240064.
[17] Icel E, Ucak T, Icel A, et al. Retinal microvascular changes in diabetic patients: OCTA findings*. Arch Basic Clin Res. 2021;3(3):94–99. doi: 10.5152/ABCR.2021.21014.
[18] Mafei L, Fiorentini A. Electroretinographic responses to alternating gratings before and after section of the optic nerve. Science. 1981;211(4485):953–955. doi: 10.1126/science.7466369.
[19] Park JC, Chau FY, Lim JI, et al. Electrophysiological and pupillometric measures of inner retina function in nonproliferative diabetic retinopathy. Doc Ophthalmol. 2019;139(2):99–111. doi: 10.1007/s10633-019-09699-2.
[20] Arden G, Hamilton A, Wilson-Holt J, et al. Pattern electroretinograms become abnormal when background diabetic retinopathy deteriorates to a preproliferative stage: possible use as a screening test. Br J Ophthalmol. 1986;70(5):330–335. doi: 10.1136/bjo.70.5.330.
[21] Falsini B, Porciatti V, Scalia G, et al. Steady-state pattern electroretinogram in insulin-dependent diabetics with no or minimal retinopathy. Doc Ophthalmol. 1989;73(2): 193–200. doi: 10.1007/BF00155037.
[22] Mermeklieva EA. Pattern electroretinography and retinal changes in patients with diabetes mellitus type 2. Neurophysiol Clin. 2019;49(3):209–215. doi: 10.1016/j.neucli.2019.04.002.
[23] Kim M, Kim RY, Park W, et al. Electroretinography and retinal microvascular changes in type 2 diabetes. Acta Ophthalmol (Copenh). 2020;98(7):e807–e13.
[24] Luu CD, Szental JA, Lee S-Y, et al. Correlation between retinal oscillatory potentials and retinal vascular caliber in type 2 diabetes. Invest Ophthalmol Vis Sci. 2010;51(1):482–486. doi: 10.1167/iovs.09-4069.
[25] Coupland SG. A comparison of oscillatory potential and pattern electroretinogram measures in diabetic retinopathy. Doc Ophthalmol. 1987;66(3):207–218. doi: 10.1007/BF00145234.
[26] Ebihara S, Machida S, Hara Y, et al. Relationships between the vascular structure and neural function of the macula in patients with diabetes mellitus. Jpn J Ophthalmol. 2021;65(1):77–88. doi: 10.1007/s10384-020-00784-7.
[27] Deng X, Li Z, Zeng P, et al. The association between decreased choriocapillary flow and electroretinogram impairments in patients with diabetes. Photodiagnosis Photodyn Ther. 2023;42:103547. doi: 10.1016/j.pdpdt.2023.103547.