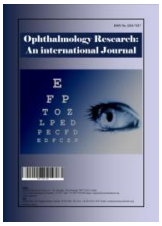

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Spectral-Domain Optical Coherence Tomography and Multifocal Electroretinography Results in the Long-Term Follow-Up of Glaucoma Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author EC designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors EC, SI and UUI managed the analyses of the study. Authors EC, KY and MCS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To investigate the changes in macular retinal layers and panretinal neuroretinal functions in the long-term follow-up of patients with primary open-angle glaucoma.
Materials and Methods: Forty-one patients diagnosed with primary open-angle glaucoma were followed up for 12 months. According to their mean deviation (MD) values), the patients were put into two groups as Group 1 with early stage glaucoma (MD≥-6) and Group 2 with middle-advanced stage glaucoma (MD<-6). Optical coherence tomography (OCT) and multifocal electroretinography (mfERG) were performed at the baseline and at the sixth- and 12th-month evaluations. The OCT, retinal layer and mfERG findings were compared between the two groups.

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Results: There was no statistically significant difference between the groups in terms of gender and age In Group 2, the mean baseline macula Retina Nerve Fiber Layer, Ganglion Cell Layer and Inner Pleksiform Layer measurements were lower in each quadrant compared to Group 1. Concerning progression in OCT measurements, there was no significant difference between the two groups. However, it was noteworthy that in Group 2, there was a decrease especially in the first and second ring amplitudes of the P1 and N2 waves and prolongation of the implicit time. At the 12-month evaluation, there was prolongation of the implicit time of the N1 wave and a decrease in the P1 wave amplitude in Group 1.

Conclusion: Retinal layers are affected in patients with intermediate and advanced stage glaucoma. In the follow-up of early stage glaucoma patients, mfERG measurements can show damage that may occur.

Keywords: Glaucoma; optic coherence tomography; multifocal electroretinography.

1. INTRODUCTION

Glaucoma is an optic neuropathy associated with the progressive loss of retinal ganglion cells and is one of the leading causes of irreversible blindness in the world [1,2]. Primary open-angle glaucoma (POAG) is a chronic, bilateral and often asymmetric optic neuropathy seen in adults, characterized by an open anterior chamber angle, intraocular pressure above 21 mmHg, acquired loss of optic nerve fibers and visual field abnormalities [3].

Advances in imaging techniques have allowed for the structural measurements of the thicknesses of the macular retinal nerve fiber layer (RNFL) and other retinal layers using spectral-domain optical coherence tomography (SD-OCT) and for the comparison of these values with electrophysiological test results [4-6]. Studies have shown that in glaucoma patients, the inner plexiform layer (IPL), especially the macular ganglion cell layer (GCL) is affected [7,8,9,10]. Strong correlations have been demonstrated between the GCL + IPL complex and multifocal electroretinography (mfERG) measurements [4,11].

The mfERG technique was first developed by Sutter and Tan in 1992 to perform the topographic measurement of retinal electrophysiological activity. As a potentially effective procedure, mfERG produces the simultaneous records of focal retinal response in many different retinal regions and shows the topographic representations of retinal response components [12,13]. The early detection of retinal dysfunction is recommended for the diagnosis of early stage glaucoma [14,15].

This study aimed to compare the changes in the SD-OCT and mfERG results of the long-term follow-up of patients with POAG. It is significant being the first study to investigate the long-term follow-up results of mfERG.

2. MATERIALS AND METHODS

Forty-seven eyes of 47 patients followed up with a diagnosis of POAG were included in the study. After the study was approved by the Clinical Research Ethics Committee, detailed information was given to each patient concerning the procedures and tests to be performed, and their written consent was obtained. A routine ophthalmologic examination was performed on all patients before enrollment. In all patients, OCT, visual field analysis, and MfERG scans were performed at the first examination (baseline) and at the sixth- and 12^{th}-months. The patients were put into two groups according to their visual field values using the Hodapp-Parrish-Anderson Glaucoma Grading Scale. Group 1 consisted of early-stage glaucoma patients with a mean deviation value of ≥-6 while Group 2 comprised middle-advanced stage glaucoma patients with a mean deviation value of <-6. The baseline values obtained by best-corrected visual acuity (BCVA), intraocular pressure, OCT, visual field and mfERG measurements were compared between the two groups. The progression of the values obtained by the OCT and mfERG measurements of the groups was also examined.

2.1 OCT Imaging and Layer Segmentation

The OCT images of the patients were obtained using the Spectralis HRA + OCT device (Heidelberg Engineering GmbH, Heidelberg, Germany). In addition to the macular thickness, a retinal layer analysis was performed using the automatic segmentation analysis of the device, and the thickness of all retinal layers were

recorded separately. Heidelberg Eye Explorer software (Version: 6.0) was used for retinal layers segmentation. Using the standard ETDRS table, the average thickness of each retinal layer was calculated within the areas corresponding to the center (r = 1 mm), inner ring (r = 1–3 mm), and outer ring (r = 3–6 mm) (Fig. 1).

The mRNFL, mGCL and mIPL layers were evaluated with the automatic segmentation of the retina with Heidelberg Spectralis HRA + OCT (Fig. 2).

All mfERG scans were performed by the same technician using the same device (Metrovision Monpack 3, Metrovision, France). The mfERG test was performed in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) criteria [16]. An image pattern consisting of 61 hexagons with dimensions adjusted to create an equal signal was used on the monitor screen, and recordings were obtained from 61 regions of the retina in approximately 5 minutes. When there was no stimulus during the test, the electrical activity and noise level were recorded, and the results with a noise level above 5 μV were not taken into consideration. In addition, the test results with loss of attention and number of rejected stimuli 20% higher than the total stimulus were not included in the study. A concentric ring analysis was undertaken, in which the first ring covered the periphery of 0-2 degrees, second ring 2-5 degrees, third ring 5-10 degrees, fourth ring 10-15 degrees, and the fifth ring 15 degrees (Fig. 3). The mean amplitude (nanovolt) and implicit time (milliseconds) were recorded for the whole ring analysis.

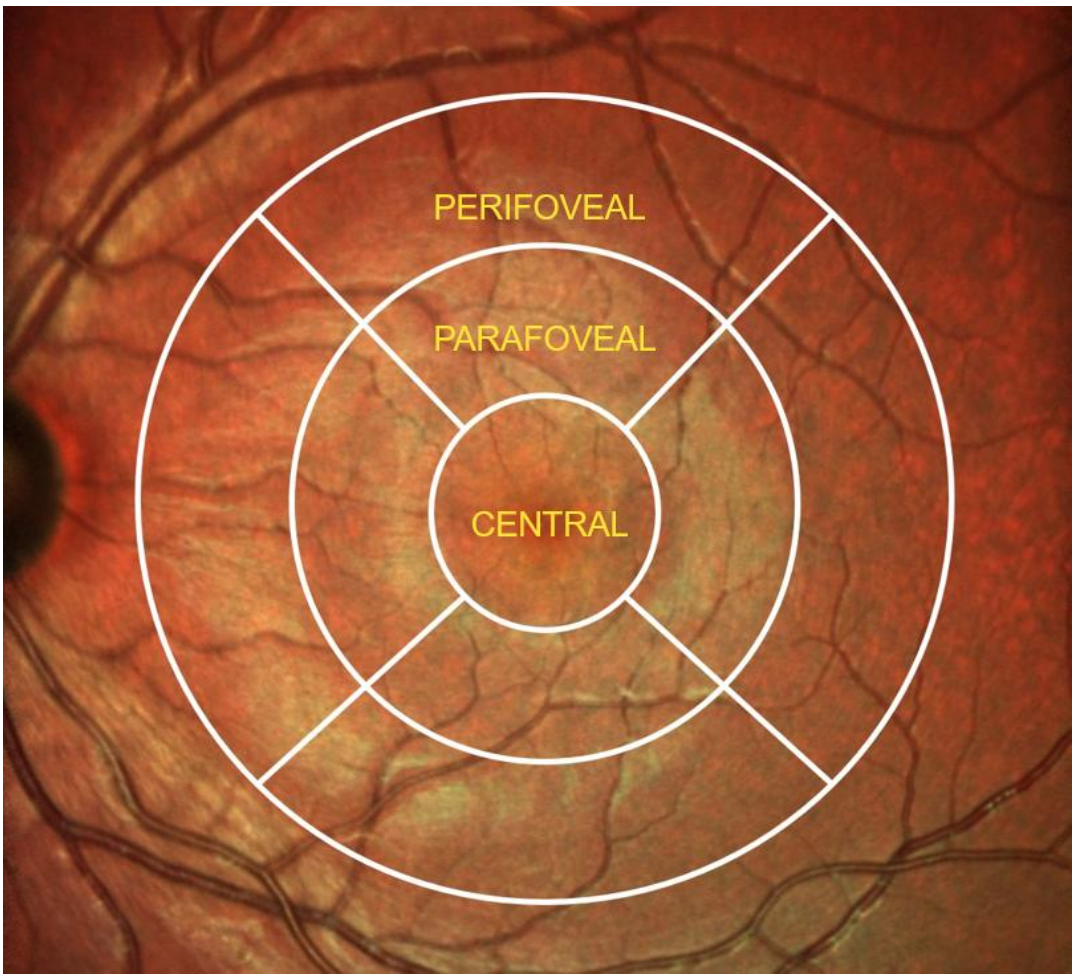

Fig. 1. A demonstrative image of the Early Treatment Diabetic Retinopathy Study macular retina ring sectors at 1, 3, and 6 mm in the central, parafoveal, and perifoveal regions

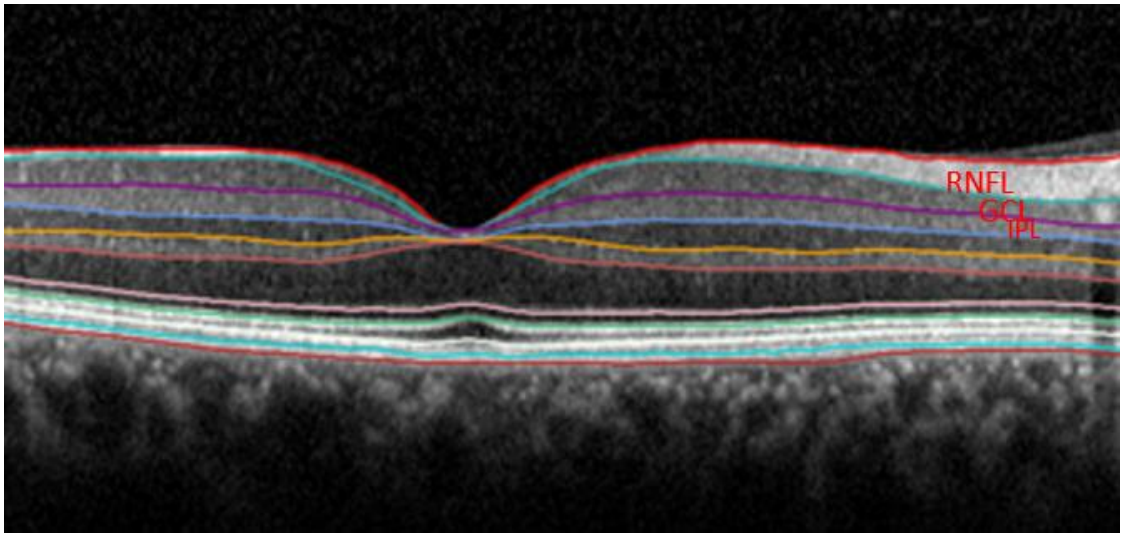

Fig. 2. Image of a retinal layer analysis of patient which can be automatically analyzed with a single horizontal foveal screen using spectral-domain optical coherence tomography and the device software

RNFL: Retinal nerve fiber layer GCL: Ganglion cell layer; INL: Inner nuclear layer; IPL: Inner plexiform layer

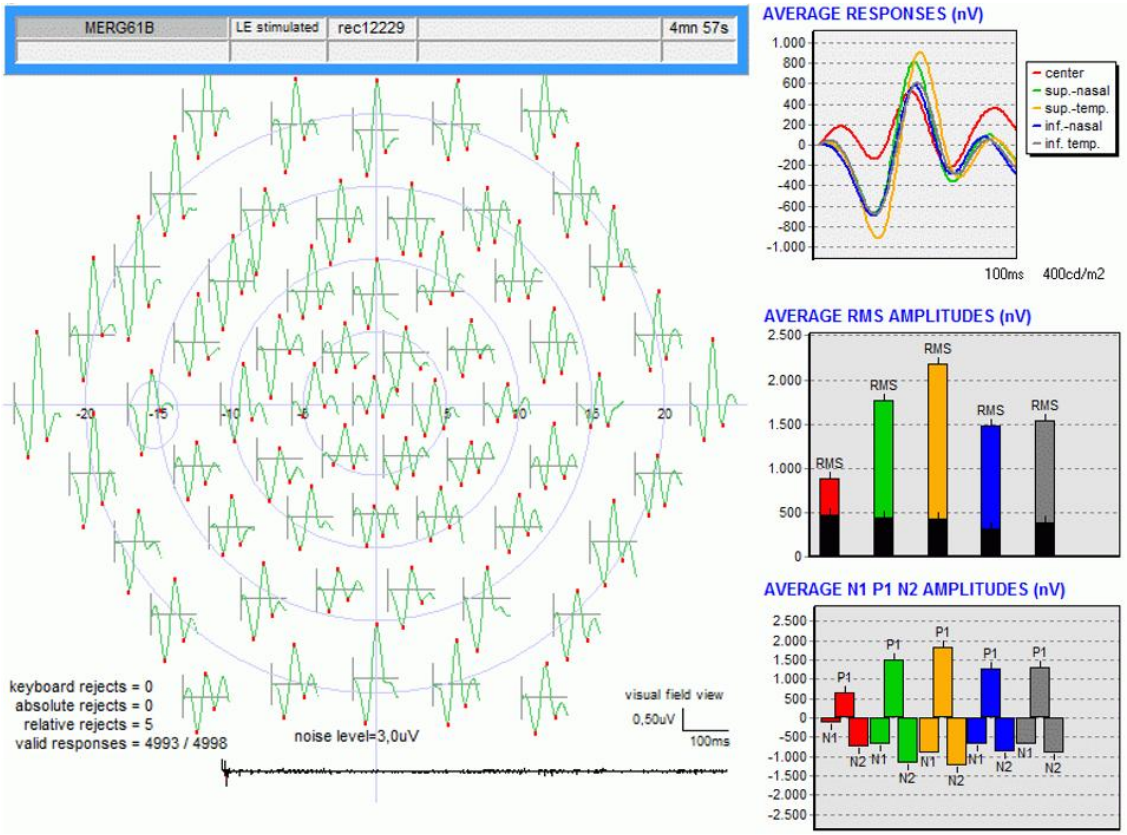

Fig. 3. Ring analysis in the mfERG test. MfERG map was divided in five rings (2°, 2°–5°, 5°–10°, 10°–15° and >15°)

2.2 Statistical Analysis

The Statistical Package for Social Science v. 17.0 (Worldwide Headquarters SPSS Inc.) was used for the statistical evaluation. For the comparison of the follow-up visual acuity, intraocular pressure, OCT and mfERG measurements with the baseline values, the general linear model and the paired samples t-test were applied. Tukey's adjustment was undertaken since there were repeated measurements, and the p value was taken as 0.05, with values below this level being accepted as significant. For the comparison of the data between the two study groups, one-way analysis of variance was used. Pearson's bivariate correlation analysis was conducted to evaluate the correlation between the data.

3. RESULTS AND DISCUSSION

Six of the 47 patients that were included in the study were excluded from further analyses due to the interruptions in their follow-up examinations or inadequate compliance with electrophysiological tests. Forty-one patients completed the study. There was no statistically significant difference in the mean deviation, IOP and BCVA values in Group 1 and Group 2 at the 12th-month evaluation compared to the baseline. The demographic characteristics of the patients are given in Table 1.

The retinal layer measurements were lower in Group 2 compared to Group 1 (Table 2); however, no significant difference was observed between the mfERG results of the two groups (Table 3). There was also no significant change in the retinal layer measurements of the two groups at the 6th and 12th months evaluation compared to the baseline (Table 4 and Table 5). When the 12th-month mfERG values of the groups were analyzed, although there was a general decrease in the N1 and P1 wave amplitudes and prolongation of the implicit time in Group 1, prolongation of the implicit time of the N1 wave and a decrease in the P1 wave amplitude were also seen (Table 6 and Table 7).

Table 1. Demographic characteristics of the patients

	Group 1	Group 2	P value
Gender (male/female)	12/11	11/7	0.383
Mean age (years)	60±6.72	62±9.27	0.196
Mean follow-up (months)	11±1.2	11±2.24	0.578
Baseline MD/dB	-2.13±0.94	-11.41±7.56	<0.01
Baseline IOP	16±1.98	15±2.63	0.132
Sixth-month IOP	16±1.95	15±1.89	0.108
12th-month IOP	16±2.36	16±2.56	0.931
Baseline BCVA	0.86±0.22	0.70±0.31	0.062
Sixth-month BCVA	0.85±0.23	0.68±0.31	0.060
12th-month BCVA	0.85±0.23	0.65±0.31	<0.05

MD: mean deviation, IOP: intraocular pressure, BCVA: best-corrected visual acuity, p: independent samples t-test

Table 2. Comparison of the baseline retinal layer measurements between the study groups

		Group 1	Group 1	P value
mRFNL	Central	12±2.74	9±3.78	<0.05
	Pericentral	22±1.61	19±2.23	<0.01
	Peripheral	34±3.06	26±7.42	<0.01
mGCL	Central	14±4.58	10±3.70	<0.01
	Pericentral	52±4.44	34±11.65	<0.01
	Peripheral	36±3.55	27±6.37	<0.01
mIPL	Central	20±4.35	17±2.77	0.01
	Pericentral	42±3.70	31±6.20	<0.01
	Peripheral	29±2.78	24±3.54	<0.01

Table 3. Comparison of the mfERG results between the study groups

		Group 1	Group 2	P
N1 amplitude	Central 2°	-51±26.44	-38±23.21	0.093
	2°-5°	-29±13.71	-30±15.43	0.824
	5°-10°	-35±60.49	-22±27.34	0.421
	10°-15°	-15±5.49	-14±5.84	0.542
	>15°	-13±5.62	-12±4.89	0.698
N1 implicit time	Central 2°	26±3.80	25±3.62	0.854
	2°-5°	25±1.45	26±2.17	0.198
	5°-10°	25±1.35	25±1.66	0.257
	10°-15°	25±1.30	25±1.29	0.247
	>15°	25±1.61	26±1.40	0.235
P1 amplitude	Central 2°	115±57.2	80±50.4	0.097
	2°-5°	70±3.70	61±6.20	0.342
	5°-10°	49±14.3	48±17.2	0.453
	10°-15°	35±10.6	33±12.3	0.624
	>15°	28±8.40	26±8.76	0.607
P1 implicit time	Central 2°	47±2.74	45±5.01	0.710
	2°-5°	44±1.42	45±2.90	0.478
	5°-10°	43±1.40	44±1.87	0.123
	10°-15°	43±1.50	44±1.34	0.056
	>15°	44±1.90	45±1.81	0.080
N2 amplitude	Central 2°	-107±57.41	-78±53.36	0.124
	2°-5°	-58±67.34	-48±27.12	0.222
	5°-10°	-39±12.63	-30±24.54	0.138
	10°-15°	-28±9.15	-26±12.54	0.549
	>15°	-19±10.08	-20±7.86	0.811
N2 implicit time	Central 2°	70±5.49	67±6.07	0.086
	2°-5°	64±1.57	65±4.75	0.404
	5°-10°	62±1.74	62±2.09	0.622
	10°-15°	62±2.56	67±8.09	<0.05
	>15°	62±2.30	62±2.06	0.864

Table 4. Comparison of the retinal layer measurements between the baseline and sixth-month evaluations

		Group 1			Group 2		
		Baseline	Sixth month	P	Baseline	Sixth month	P
mRNFL	Central	12±2.74	12±3.38	0.628	9±3.78	9±3.20	0.819
	Pericentral	22±1.61	22±2.04	0.737	19±2.23	19±1.99	0.270
	Peripheral	34±3.06	34±3.03	0.931	26±7.42	25±6.84	<0.05
GCL	Central	14±4.58	14±4.94	0.382	10±3.70	10±2.78	0.749
	Pericentral	52±4.44	51±4.76	0.331	34±11.65	33±11.05	<0.05
	Peripheral	36±3.55	35±3.15	0.408	27±6.37	27±7.44	0.854
IPL	Central	20±4.35	20±4.66	1	17±2.77	17±3.38	0.575
	Pericentral	42±3.70	42±3.35	0.942	31±6.20	30±5.80	0.414
	Peripheral	29±2.78	30±2.52	0.315	24±3.54	25±3.94	0.091

Table 5. Comparison of the retinal layer measurements between the baseline and 12th-month evaluations

		Group 1			Group 2		
		Baseline	12th month	P	Baseline	12th month	P
mRNFL	Central	12±2.74	12±3.03	<0.05	9±3.78	9±3.38	0.336
	Pericentral	22±1.61	21±1.77	0.293	19±2.23	19±2.19	0.903
	Peripheral	34±3.06	34±2.17	0.826	26±7.42	25±8.50	0.113
GCL	Central	14±4.58	14±4.89	0.255	10±3.70	9±2.96	0.477
	Pericentral	52±4.44	51±4.53	0.193	34±11.65	33±11.54	0.151
	Peripheral	36±3.55	35±2.1	0.175	27±6.37	27±7.65	1
IPL	Central	20±4.35	20±4.76	0.649	17±2.77	16±2.70	0.609
	Pericentral	42±3.70	41±2.94	0.808	31±6.20	30±5.90	<0.05
	Peripheral	29±2.78	30±2.30	0.689	24±3.54	24±4.10	0.549

Table 6. Comparison of the mfERG results between the baseline and sixth-month evaluations

		Group 1			Group 2		
		Baseline	Sixth month	P	Baseline	Sixth month	P
N1 amplitude	Central 2°	-51±26.44	-45±22.76	0.170	-38±23.21	-31±26.84	0.231
	2°-5°	-29±13.71	-31±11.61	0.691	-30±15.43	-23±14.49	0.053
	5°-10°	-35±6.49	-23±6.72	0.371	-22±27.34	-22±8.50	0.395
	10°-15°	-15±5.49	-16±5.01	0.662	-14±5.84	-15±5.52	0.841
	>15°	-13±5.62	-13±3.71	0.749	-13±3.79	-13±3.71	0.966
N1 implicit time	Central 2°	26±3.80	26±3.04	0.593	25±3.62	25±2.99	0.864
	2°-5°	25±1.45	25±1.71	0.393	26±2.17	26±1.91	0.126
	5°-10°	25±1.35	25±1.44	0.929	25±1.66	26±1.53	0.375
	10°-15°	25±1.30	25±1.40	0.727	25±1.29	25±1.75	0.515
	>15°	25±1.61	25±1.54	0.198	26±1.40	26±1.76	0.173
P1 amplitude	Central 2°	115±57.2	103±52.9	0.106	80±50.4	65±45.5	0.054
	2°-5°	70±3.70	71±5.94	0.802	61±6.20	56±27.7	0.085
	5°-10°	49±14.3	50±15.7	0.522	48±17.2	45±18.0	0.281
	10°-15°	35±10.6	38±10.6	0.190	33±12.3	35±13.3	0.969
	>15°	28±8.40	28±9.00	0.761	26±8.76	27±10.63	0.614
P1 implicit time	Central 2°	47±2.74	47±3.17	0.721	45±5.01	45±3.17	0.781
	2°-5°	44±1.42	44±1.70	0.609	45±2.90	45±1.93	0.404
	5°-10°	43±1.40	43±1.54	0.345	44±1.87	45±1.82	0.141
	10°-15°	43±1.50	43±1.73	0.685	44±1.34	45±2.12	0.125
	>15°	44±1.90	44±1.77	0.875	45±1.81	45±2.16	0.694
N2 amplitude	Central 2°	-107±57.41	-101±53.59	0.331	-78±53.36	-59±43.08	0.048
	2°-5°	-58±67.34	-63±27.10	0.439	-48±27.12	-46±26.99	0.360
	5°-10°	-39±12.63	-40±14.71	0.640	-30±24.54	-32±17.92	0.839
	10°-15°	-28±9.15	-30±9.95	0.290	-26±12.54	-31±12.39	0.158
	>15°	-19±10.08	-21±8.86	0.152	-20±7.86	-22±10.1	0.227
N2 implicit time	Central 2°	70±5.49	68±4.31	0.224	67±6.07	67±6.92	0.940
	2°-5°	64±1.57	61±1.94	0.314	65±4.75	66±7.69	0.383
	5°-10°	62±1.74	61±1.56	0.484	62±2.09	63±2.66	0.108
	10°-15°	62±2.56	61±2.31	0.259	67±8.09	62±1.80	0.447
	>15°	62±2.30	61±2.14	0.637	62±2.06	62±2.39	0.851

Table 7. Comparison of the mfERG results between the baseline and 12th-month evaluations

		Group 1			Group 2		
		Baseline	**12th month**	**P**	**Baseline**	**12th month**	**P**
N1 amplitude	Central 2°	-51±26.44	-39±21.09	0.041	-38±23.21	-38±29.31	0.944
	2°-5°	-29±13.71	-25±12.01	0.088	-30±15.43	-25±9.84	0.375
	5°-10°	-35±6.49	-19±7.34	0.278	-22±27.34	-19±10.14	0.203
	10°-15°	-15±5.49	-14±5.48	0.416	-14±5.84	-16±5.21	0.098
	>15°	-13±5.62	-11±2.67	0.016	-12±4.89	-12±3.97	0.792
N1 implicit time	Central 2°	26±3.80	26±3.32	0.650	25±3.62	26±2.63	0.371
	2°-5°	25±1.45	26±1.73	0.014	26±2.17	25±1.48	0.592
	5°-10°	25±1.35	25±1.61	0.006	25±1.66	25±1.18	0.835
	10°-15°	25±1.30	25±1.47	0.742	25±1.29	25±1.54	0.228
	>15°	25±1.61	26±1.85	0.024	26±1.40	25±1.42	0.771
P1 amplitude	Central 2°	115±57.2	92±54.0	0.05	80±50.4	73±43.4	0.511
	2°-5°	70±3.70	60±22.8	0.025	61±6.20	53±20.0	0.379
	5°-10°	49±14.3	45±14.0	0.277	48±17.2	44±13.6	0.607
	10°-15°	35±10.6	30±7.95	0.038	33±12.3	36±12.1	0.060
	>15°	28±8.40	23±7.2	0.013	26±8.76	27±8.63	0.443
P1 implicit time	Central 2°	47±2.74	47±3.68	0.525	45±5.01	43±8.22	0.343
	2°-5°	44±1.42	45±1.59	0.025	45±2.90	44±8.12	0.439
	5°-10°	43±1.40	44±1.35	0.016	44±1.87	43±7.66	0.585
	10°-15°	43±1.50	44±1.61	0.308	44±1.34	40±10.1	0.232
	>15°	44±1.90	44±1.84	0.191	45±1.81	43±7.47	0.369
N2 amplitude	Central 2°	-107±57.41	-101±52.59	0.763	-78±53.36	-56±38.81	0.114
	2°-5°	-58±67.34	-55±20.82	0.849	-48±27.12	-45±17.67	0.212
	5°-10°	-39±12.63	-35±11.60	0.067	-30±24.54	-34±11.62	0.305
	10°-15°	-28±9.15	-24±7.59	0.064	-26±12.54	-27±8.24	0.604
	>15°	-19±10.08	-18±6.70	0.593	-20±7.86	-20±6.91	0.631
N2 implicit time	Central 2°	70±5.49	70±5.03	0.929	67±6.07	65±6.13	0.337
	2°-5°	64±1.57	64±1.87	0.485	65±4.75	65±6.05	0.627
	5°-10°	62±1.74	62±1.63	0.481	62±2.09	66±8.80	0.220
	10°-15°	62±2.56	62±2.08	0.693	67±8.09	65±6.81	0.435
	>15°	62±2.30	63±6.04	0.383	62±2.06	65±7.56	0.259

4. CONCLUSION

In this study, we performed the long-term follow-up of early-stage and middle-advanced stage glaucoma patients and compared their results. By evaluating the results of the macular retinal layers in glaucoma patients, we aimed to determine whether mfERG would be useful in early and mid-advanced stages in the diagnosis and follow-up. It is known that retinal layers are generally affected in middle-advanced stage glaucoma, and these effects are mostly seen on GCL and RNFL. When our study groups were compared, the macular RNFL, GCL and IPL in all areas were found to be thinner in middle-advanced stage glaucoma. However, there was no significant change in the long term follow-up of the two groups. We attributed this to the patients attending their controls regularly and not disrupting their medical treatments.

In glaucoma progression, when GCL disappear, OCT has the ability to objectively measure the decreased RNFL thickness [17]. Studies have shown that there are morphological changes in the macular area, and macular OCT may be more sensitive than the measurements of the peripapillary nerve fiber layer in evaluating progressive glaucomatous retinal damage [18]. It has been suggested that there is no significant difference in the early glaucoma detection capability of GCL and IPL thicknesses in adults with glaucoma compared to mRNFL and peripapillary RNFL [19,20]. Recent studies have reported that macular parameters, such as the ganglion cell complex (GCC = macular RNFL + GCL + IPL]) improve the diagnostic power of

OCT for glaucoma [19,21,22] Moura et al. found that there was thinning in the GCL and IPL layers in glaucoma patients with severe visual field loss [23]. In their SD-OCT study, Lee et al. found significant thinning in all quadrants of the outer ring in the subfield of ETDRS in the GCL-IPL complex and in the macular RNFL layer in the analysis of glaucoma patients compared to the control group [24]. Our results were also correlated with these studies, supporting that the mRNFL, GCL and IPL layers are very important indicators of glaucoma progression.

As a potentially effective procedure, mfERG evaluates the simultaneous recording of focal responses in many different retinal regions and allows for the derivation of topographic recordings of retinal response components [25,26]. The typical waveform of a basic mfERG response is a biphasic wave with an initial negative deflection (N1) followed by a positive peak (P1). After the positive peak, there is usually a second negative deviation (N2). In addition to a standard examination, Brandao et al. applied visual field analysis, GCL-IPL complex measurement, and the 2F-mfERG test to the participants in their study and evaluated the relationship of these findings with each other. The authors determined that in patients with early-stage glaucoma, the 2F-mfERG and GCL-IPL tests were the diagnostic tools with the highest probability of detecting glaucomatous dysfunction, and combining functional and structural tests is valuable in terms of early diagnosis [11]. Similarly, Talamini et al. [27] showed that although the use of OCT segmentation analysis in glaucoma was beneficial in increasing OCT sensitivity, there were still many patients with normally appearing retinas, but mfERG was able to document retinal dysfunction in these patients and combining these two tests had diagnostic value. These studies confirm the presence of a non-linear relationship between structural and functional damage at different stages in glaucoma; that is, structural damage may not correlate with functional damage; however, the use of mfERG in these cases remains unclear. Gölemez et al. measures the sensitivity of mfERG in diagnosis, especially in suspected cases. The authors observed that especially the N2 amplitudes were decreased in the central ring (5 degrees) in the early stage and in all rings in advanced-stage patients compared with the control group [15]. In our study, when the mfERG parameters of the patients were compared between the early and middle-advanced glaucoma groups, there was no significant difference in the amplitudes of the N1-P1-N2 waves and implicit time. There was also no significant difference in middle-advanced stage cases between the baseline and 12^{th}-month measurements; however, statistically significant differences were observed in the amplitude and implicit time measurements of the N1 and P1 waves, among the patients with early-stage glaucoma. The early-stage changes, especially in the N1-P1 waves up to the central 10 degrees may be an indicator of progression in this patient group. Longer studies are required to support this idea.

In conclusion, in our study, in addition to SD-OCT measurements, mfERG did not reveal any significant change in retinal layers in the long-term follow-up. However, the abnormal mfERG results in early-stage glaucoma patients suggest that this modality can predict glaucomatous damage that may develop in this patient group and would be useful in their follow-up.

CONSENT AND ETHICAL APPROVAL

Forty-seven eyes of 47 patients followed up with a diagnosis of POAG were included in the study. After the study was approved by the Clinical Research Ethics Committee, detailed information was given to each patient concerning the procedures and tests to be performed, and their written consent was obtained

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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