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ORIGINAL ARTICLE

Pattern electroretinography and retinal changes in patients with diabetes mellitus type 2

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Summary
Objectives. — To objectively explore retinal neuronal function by pattern electroretinography (PERG) in patients with diabetes mellitus (DM) type 2 at different stages of diabetic retinopathy (DR).
Methods. — A group of 84 patients with DM was studied, divided into three subgroups according to the degree of retinal changes. The first subgroup consisted of patients without DR ($n = 28$), the second patients with initial DR ($n = 27$) and the third patients with advanced DR ($n = 29$). Controls were 47 healthy individuals. PERG was performed and latency and amplitude were analyzed.
Results. — PERG results were affected in DM patients including the group without DR; abnormalities were more severe in patients with advanced DR.
Conclusion. — PERG could be used as an objective method providing evidence of early changes in retinal neuron function in DM patients, including at preclinical stages. It is useful for monitoring disease progression, as it is non-invasive, harmless, rapid, inexpensive and readily repeatable.

Introduction

Diabetes mellitus (DM) is a socially significant disease affecting millions of people around the world. According to the International Diabetes Federation in 2017, at least 451 million people worldwide suffer from DM. This number is expected to increase, by 2045 their number being estimated to reach 693 million [3,13]. Diabetic changes in vision are related to ophthalmoscopic or angiofluorographic visible changes in the retina, so-called diabetic retinopathy (DR), which is a form of microangiopathy. From a functional point of view, the retina is a vascularized neuronal

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Table 1 Distribution of patients with mean age and duration of DM in the different groups.

	Number of patients	Mean age (years)	Duration of DM (years)
Controls	47	38.6 ± 12.4	0
DM without DR	28	40.0 ± 13.9	6.8 ± 4.2
DM with initial DR	27	43.3 ± 11.6	9.3 ± 2.2
DM with advanced DR	29	45.2 ± 14.4	11.6 ± 4.6

DM: diabetes mellitus; DR: diabetic retinopathy.

tissue; the modern concept of retinopathy involves both retinal neurodegeneration and microvascular complications [4,8]. Recent opinion states that DR may be considered as a neurodegenerative disease before the vascular changes are evident [24]. In this context, there is renewed interest in electrophysiological methods for early diagnosis of neurodegenerative changes in glaucoma and DM. Pattern electroretinography (PERG) is used for the objective study of the retinal neuronal function. It detects the activity of the retinal ganglion cells and reflects the integrity of the three neurons in the retina: photoreceptors, bipolar and ganglion cells [15,25].

The aim of the present study was to objectively explore retinal neuronal function by PERG in patients with DM type 2 at different stages of DR.

Methods

This prospective study was performed over 3 years (2014—2017) and met the criteria of standards for good medical practice. It was carried out with the informed consent of all participants in compliance with all ethics standards under the Helsinki Declaration (2013).

Inclusion criteria were: patients with type 2 DM with and without DR, acceptable refractive errors up to 2 dpt. Exclusion criteria were: Glaucoma, senile macular degeneration, advanced cataract, vascular eye diseases, optic neuritis, refractive errors more than 2 dpt., amblyopia, laser therapy. Patients with multiple sclerosis, Parkinson's disease, epilepsy, dementia, or brain tumor were also excluded.

Patients

The study included a series of 84 patients with DM, divided into three groups according to the severity of retinal changes. The first group consisted of 28 patients without DR and normal best-corrected visual acuity (BCVA) (LogMar score 0.00 ETDRS Early Treatment Diabetic Retinopathy Study) and acceptable refractive errors ± 2 dpt. The mean DM duration was 6.8 ± 4.2 years. The second group consisted of 27 patients with initial DR (i.e. with first or second stage of non-proliferative DR (NPDR), mild to moderate according to the clinical classification of the American Academy of Ophthalmology AAO) [1]. The mean DM duration was 9.3 ± 2.2 years. The third group consisted of 29 patients with advanced DR (i.e. with third stage of NPDR (severe) or first stage of proliferative DR (early), according to the AAO classification, as well as patients with macular edema or macular ischemia). The mean DM duration was 11.6 ± 4.6 years. The patients with DR had BCVA up to LogMar score 0.1 ETDRS (in case of lower vision, PERG is not informative enough and flash stimulation should be performed) and acceptable refractive errors ± 2 dpt. Fluorescein angiography (FA) and optical coherent tomography (OCT) were used for the classification of the different groups. We studied both eyes in all patients but decided to analyze only right eye results, to prevent confounding results from inter-eye correlation which doubles the sample size and increases the probability of false positive results. The mean age and DM duration in the different groups are presented in Table 1.

Laboratory tests for blood sugar level, HbA1c and lipid levels were performed additionally. During the PERG study the patients were in a normoglycemic condition (blood sugar levels between 4.0—6.1 mmol/l).

Controls were 47 healthy individuals (26 women and 21 men with an average age of 38.6 years) with normal BCVA (LogMar score 0.00 ETDRS) and acceptable refractive errors ± 2 dpt, without any known ophthalmological or neurological disease as well as other systemic diseases.

Method of PERG

All studies of PERG were performed in a specially equipped certified electrophysiological laboratory. Standard ''Neuro-MEP 4'' equipment (Neurosoft, Ivanovo, Russia), was used. The study was performed with a three-channel recording with equipment adjustments according to ISCEV standards for PERG (2013) [2,6]. The main variables considered in the present study were PERG latency and amplitude.

Patients were in a sitting position. The distance to the monitor was 100 cm. Patients were examined with the appropriate optical correction for that distance if necessary, under mesopic conditions, identical in all patients, without mydriasis. We used a classic cathode stimulator with a contrast-reversing pattern from black to white and vice-versa with an equal number of black and white squares in a checkboard, with standard individual width of 1° for a stimulating field of 30° for peripheral stimulation and 0.25° for a stimulating field of 15° for central stimulation. The study was binocular, as this is considered more stable. A standardized silver fiber active electrode (Cornea) was used. It was placed in contact with the globe after local topical anesthesia. The reference electrode was placed on the ear, and the ground electrode on the right wrist. The impedance between the recording and the ground electrode was less than 5 kΩ. The reversal frequency was 2 Hz, which corresponded to 4 reversals per second (rps). The generated signal passed through a standardized amplifier

Table 2 Comparative analysis of PERG components (montage right cornea-A2).

Component	Stim.	Controls ($n = 47$)		DM without DR ($n = 28$)		P	DM with initial DR ($n = 27$)		P	DM with advanced DR ($n = 29$)		P
		Mean	SD	Mean	SD		Mean	SD		Mean	SD	
N35 latency	15°	31.07	5.48							38.92	14.97	0.016
N35 latency	30°	28.25	4.60							35.28	13.95	0.021
P50 latency	15°	52.73	3.84				60.75	14.22	0.013	66.09	16.13	≤ 0.001
P50 latency	30°	51.53	3.83				55.34	9.49	0.045	61.60	9.74	≤ 0.001
N35-P50 amplitude	15°	1.96	0.55	1.56	0.81	0.005	1.44	0.88	0.007	1.13	0.68	≤ 0.001
N35-P50 amplitude	30°	2.20	0.65	1.93	0.92	0.099	1.50	0.73	≤ 0.001	1.59	0.99	0.006
P50-N95 amplitude	15°	4.13	1.65	3.19	1.60	0.026	2.90	1.64	0.001	1.92	0.98	≤ 0.001
P50-N95 amplitude	30°	4.54	1.59	3.52	1.72	0.005	3.33	1.45	0.002	2.36	1.21	≤ 0.001

DM: diabetes mellitus; DR: diabetic retinopathy; Stim.: stimulation..

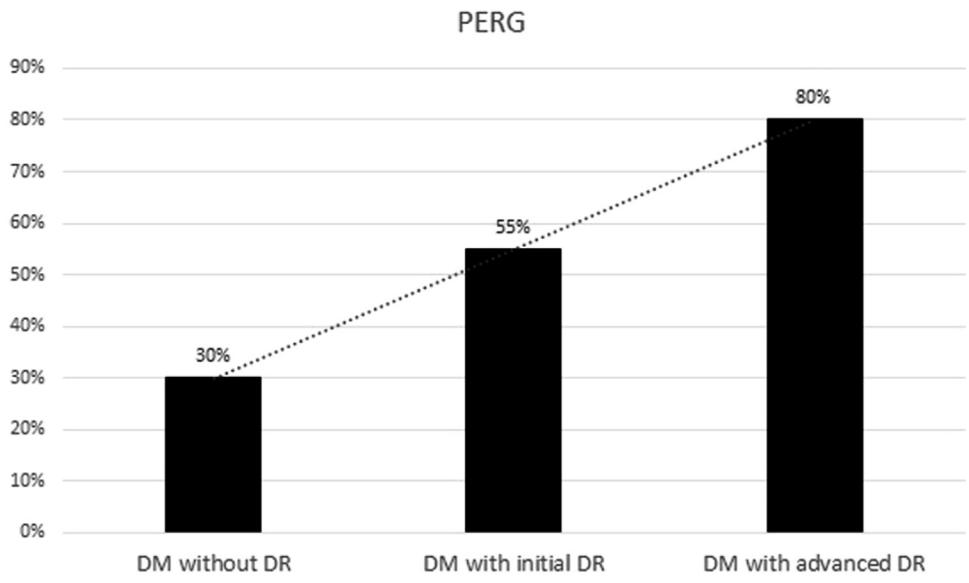

Figure 1 Percentage of altered Pattern electroretinography (PERG) variables in the different groups of patients, according to the evolution of Diabetic retinopathy (DR) severity.

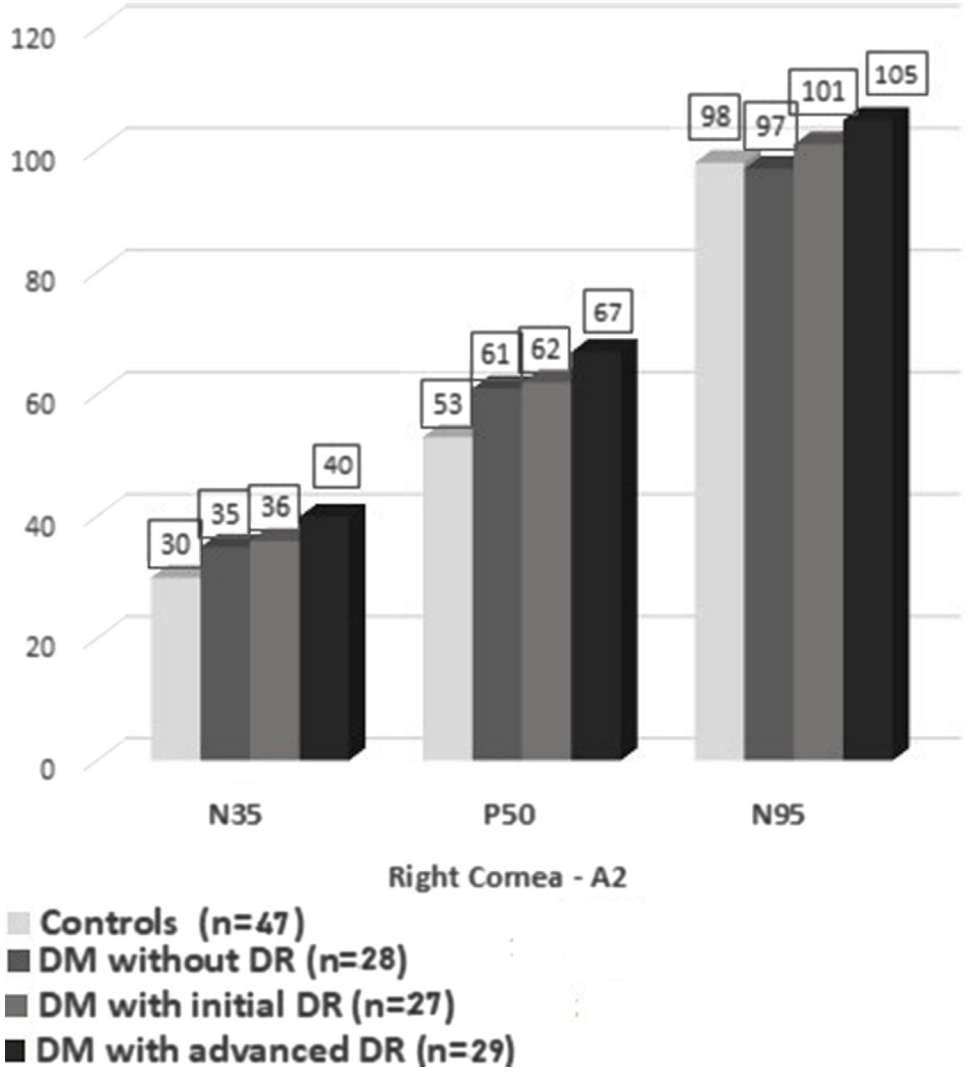

Figure 2 Prolongation of Pattern electroretinography (PERG) latencies with the advance of the retinal changes.

with a minimum input impedance of 10 MΩ. The recording frequency of the amplifier ranged from 1 to 100 Hz. An additional digital filtration with a frequency band of 1—30 Hz was carried out. The amplifier was electrically isolated and met current safety standards. A minimum of 100 artefact-free sweeps were averaged, the sweep time was 300 ms with 4 rps stimulation rate and 250 ms between reversals. The system was equipped with automatic rejection of artefacts with amplitude ± 100 μV and a minimum sampling rate of 1000 Hz. The program had a setting for automatically blinking artifacts removal. At least two trials were carried out to confirm the reproducibility of the obtained curves. The analysis was based on the latency and amplitude of components N35, P50 and N95.

Statistical analysis was performed with IBM SPSS Statistics 23.0 statistical package. Descriptive statistical analysis was used, based on the calculation of the median and percentiles from the observed sample distribution with 95% reference interval as a limit of normal. The Refval program was used for calculating the laboratory normal ranges. Variation and comparative analyzes were also performed.

Results

We performed a comparative analysis between the different groups of DM patients and controls regarding PERG components. Potential confounding factors, such as sex and age showed no significant difference between the study groups.

A significant difference was found between DM patients without DR and controls in PERG amplitude component P50-N95 at 15° and 30° and N35-P50 component at 15°. The diabetic patients had significantly longer N35 component latency (Table 2).

A significant difference was found between DM patients with initial DR and controls in P50 latency component at 15° and 30° and amplitude components (N35-P50 and P50-N95) at 15° and 30°. Diabetic patients had significantly longer P50 latency and lower PERG amplitude (Table 2).

A significant difference was found between DM patients with advanced DR and controls in all latency (N35 and P50) and amplitude components (N35-P50 and P50-N95) at 15° and 30°. Diabetic patients had significantly longer PERG latency and lower amplitude (Table 2).

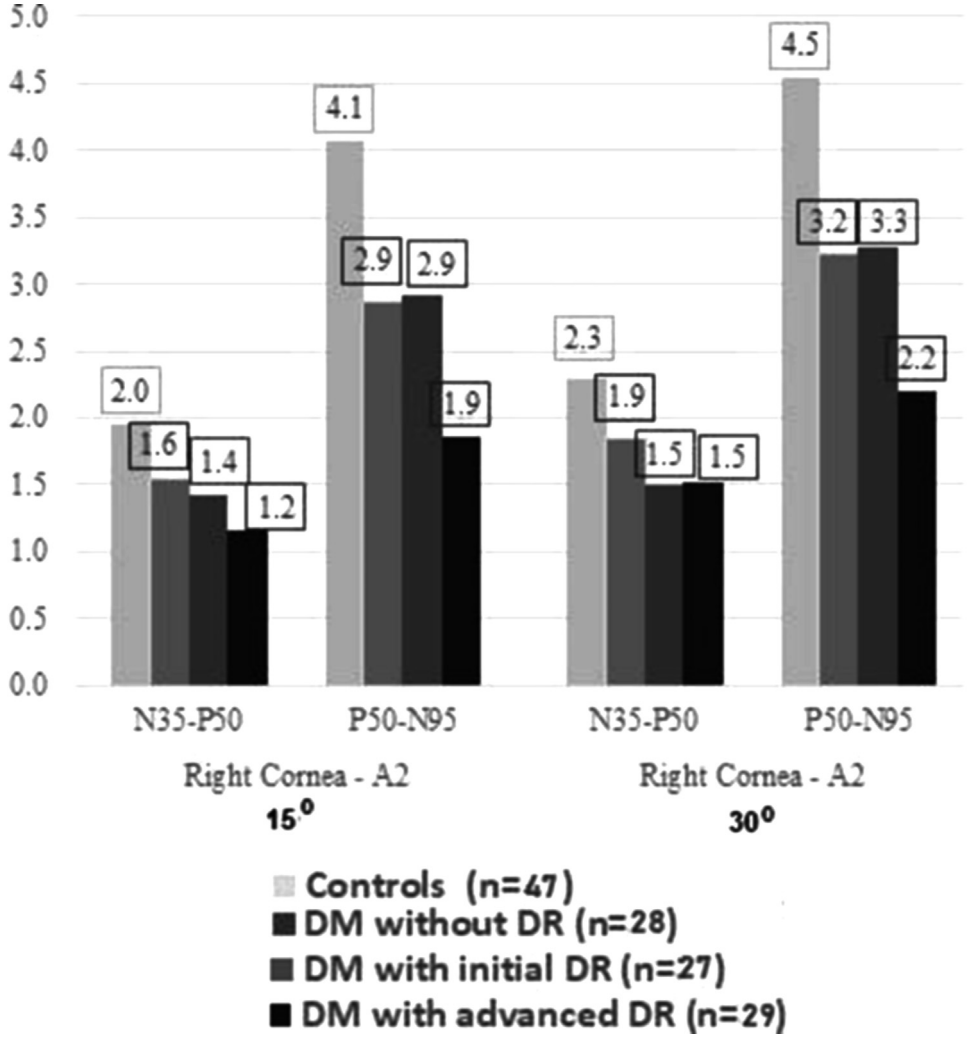

Figure 3 Reduction of Pattern electroretinography (PERG) amplitudes with the advance of the retinal changes.

Changes in PERG components were more distinct in patients with initial DR and were maximal in patients with advanced DR. The percentages of abnormal components are presented in Fig. 1 in the different groups of patients. Figs. 2 and 3 shows that all PERG components are more altered (prolonged latencies and reduced amplitudes) as the retinal changes induced by DM are more severe.

Discussion

Our results demonstrated significant alterations in most of PERG components, associated with degree of severity of DR. It is known that P50 and N95 components reflect activity of retinal ganglion cells [16,20]. Their alteration in DM patients even without overt DR suggests initial neuronal dysfunction, despite the absence of signs of vascular damage in the retina. Our results found that changes in PERG amplitude occur first in the course of DR including at a preclinical stage, with later changes in PERG latency when DR is more advanced.

The review of the available literature shows contradictory results [10,21,22]. Changes in PERG components in patients with DM without DR were reported by some authors [17—19,27,29], especially P50 or N95 amplitude decrease [11,23,26], correlated with the degree of retinal impairment. Latency prolongation and amplitude reduction worsen as the retina is more damaged. Conversely, for other authors, PERG changes occur only with overt signs of DR [5], due to the presence of soft exudates, without finding any PERG changes in DM patients without DR [7,9,12]. In any case, PERG could be used as a screening for DR progression, with more changes in patients with proliferative DR and who received laser therapy. It was suggested that PERG could be used as a screening test for patients requiring strict ophthalmological control [14,28].

Our results indicate that PERG could be used for early detection of subclinical changes in retinal neuron function occurring as a complication of DM. They demonstrate that neurodegenerative changes occur very early in diabetic patients, before the presence of any visible changes in the retina, indicating that functional changes in vision in diabetic patients arise before structural ones. This finding is very important given the development of new drugs with neuroprotective action, since until now DR therapy has been mainly directed against the vascular changes.

In conclusion, PERG could be used as an objective method providing evidence of early changes in the retinal neuron function, including preclinical screening. It is an ideal test for monitoring disease progression, as it is non-invasive, harmless, rapid, inexpensive and readily repeatable.

Disclosure of interest

The author declares that she has no competing interest.

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