Dynamics of Changes in Visual Evoked Potentials Values with the Advance of Retinal Changes in Patients with Diabetes Mellitus

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Abstract: Aim: *The aim of the study was to explore objectively the visual analyzer (VA) function by pattern visual evoked potentials (PVEPs) in patients with diabetes mellitus (DM) in different stages of diabetic retinopathy (DR) and to compare the results with controls and between the different groups.*

Material and methods*: This is a prospective observation study with 3-year duration (2014-2017). A group of 185 people was studied. Patients with DM were 138. They were divided into two main groups - patients without DR and patients with DR. The first group consisted of two subgroups – patients with newly-diagnosed DM (33 people) and patients with DM duration longer than 1 year (mean DM duration 6.8 ± 4.2 years) (36 people). The second main group consists of patients with DR, divided into two subgroups – patients with initial DR (34 people) and patients with advanced DR (35 people). Controls for the EF studies were 47 healthy individuals. PVEPs were performed. The main variables that were considered in the results analysis were the latency and amplitude, reflecting the configuration of the wave forms.*

Results*: PVEPs results were affected even in patients without DR. The changes in PVEPs values became more distinct in patients with initial DR group as a number of components with significant difference as well as a degree of significant difference, to reach their maximum number and significance manifestation peak in patients with advanced DR, the most affected by DM group.*

Conclusion: *PVEPs studies could be used as an objective methods for registration of early changes in the VA function as a DM complication. Also, to monitor the changes in dynamics as they are non-invasive, harmless, fast, inexpensive and repeatable.*

Keywords*: Visual evoked potentials, Diabetes mellitus, Diabetic retinopathy.*

Introduction

Diabetes mellitus (DM) is a socially significant disease affecting millions of people around the world. According to the World Health Organization (WHO) by 2014 at least 422 million people worldwide (8.5% of the adult population) suffer from DM. This number is expected to increase, by 2030 their number will reach 522 million [25].

Usually we speak about diabetic changes in vision when we can detect ophthalmoscopic or angiofluorographic visible changes in the retina so-called diabetic retinopathy (DR). It is manifestation of microangiopathy. But from a functional point of view, the retina is a vascularized neuronal tissue. In addition, in order to have a clear image, it is necessary for the entire visual path to the cortex to function properly. This is the reason why the modern concept

of retinopathy involves retinal neurodegeneration and microvascular complications [5, 6, 8]. Visual evoked potentials (VEPs) are used for objective studying the VA function. VEPs depend on the functional integrity of the entire visual pathway from the retina through the optic nerve, the optic tract, the optical radiation to the visual cortex [12, 15, 22].
The aim of the study was to explore objectively the visual analyzer (VA) function by pattern visual evoked potentials (PVEPs) in patients with DM in different stage of DR and to compare the results with controls and between the different groups.

Material and methods

This is a prospective observation study with 3-year duration (2014-2017). A group of 185 people (370 eyes) was studied. The patients with DM were 138 (276 eyes) with an average age of 41.5 ± 13.96 years. The patients were divided into two main groups according to the presence of DR. The first group consisted of patients without DR – 69 patients with normal best corrected visual acuity (BCVA) (LogMar score 0.00 ETDRS (Early Treatment Diabetic Retinopathy Study) and acceptable refractive errors ± 2 dpt. This group was divided into two subgroups. The first one consisted of patients with newly-diagnosed DM – 33 people (as newly-diagnosed we classify DM, diagnosed over the last one year). The second subgroup consisted of 36 patients without DR with DM duration longer than 1 year (mean DM duration 6.8 ± 4.2 years). The second main group consists of patients with DR – 69 people, divided into two subgroups – patients with initial DR (as initial DR we classify patients with first and second stage of nonproliferative DR (NPDR) – mild and moderate, according to the clinical classification of the American Academy of Ophthalmology (AAO) [2] – 34 people. The second subgroup consisted of patients with advanced DR (as advanced DR we classify patients with third stage of NPDR (severe) and first stage of proliferative DR (early), according to the AAO classification – 35 people. Patients with DR had BCVA up to LogMar score 0.1 ETDRS (in case of lower vision, this study is not informative enough and flash stimulation should be performed) and acceptable refractive errors ± 2 dpt. None of the patients underwent laser therapy, because it affected the bioelectric signal. Every group consisted of patients with type 1 and type 2 DM.

Controls for the EF studies were 47 healthy individuals with normal BCVA and without any known ophthalmological or neurological disease as well as other systemic diseases. The control group included individuals of an average age of 38.57 years – 21 males and 26 females.

The patients were examined clinically by full ophthalmologic examination, fluorescein angiography (FA), optical coherent tomography (OCT), electrophysiologically by PVEPs. Laboratory tests for blood sugar level, HgA1c and lipid levels were performed additionally. During the PVEPs study the patients were in normoglycemic condition (blood sugar levels between 4.0-6.1 mmol/l). The study meets 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 Helsinki Declaration (2013).

Inclusion criteria
Patients with type 1 and type 2 DM with and without DR, with refractive errors up to 2 dpt.

Exclusion criteria
Glaucoma, senile macular degeneration, advanced cataract, vascular eye diseases, optic neuritis, refractive errors more than 2 dpt, amblyopia. Multiple sclerosis, Parkinson's disease, epilepsy, dementia, and brain tumor were excluded by neurologists.

Method of PVEPs

All studies of PVEPs were performed in a specially equipped certified electrophysiological laboratory. Standardized four channels equipment "Neuro-MEP 4" produced by Neurosoft Company, was used. The study was performed with a three-channel recording with equipment adjustments according to the latest published ISCEV standards for PVEPs (2016) [3, 20]. The main variables that were considered in the analysis of PVEPs in the present study were latency (L) and amplitudes (A), reflecting the configuration of the wave forms.

The patients were in a sitting position. The distance to the monitor was 100 cm. The patients were examined with the appropriate optical correction for that distance if it was 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 periferal stimulation and 0.25° for a stimulating field of 15° for central stimulation.

We performed monocular PVEPs stimulation. The active electrodes were placed on the scalp at standard locations, depending on the head size, according to the International System 10/20 – at Oz (above the visual cortex – along the midline, about 3cm above the inion) and two lateral occipital electrodes, placed horizontally at 3 cm to the right and to the left of Oz (about 5% from Oz) – O1 and O2. The reference electrode was at Fz (along the midline fronthally – about 12 cm above the nasion) and the ground electrode was placed on the right wrist. The frequency reversion was 1 Hz, which corresponds to 2 reversals per second (rps) [20]. We analyzed the L and A of components P50, N75, P100, N145 and P200.

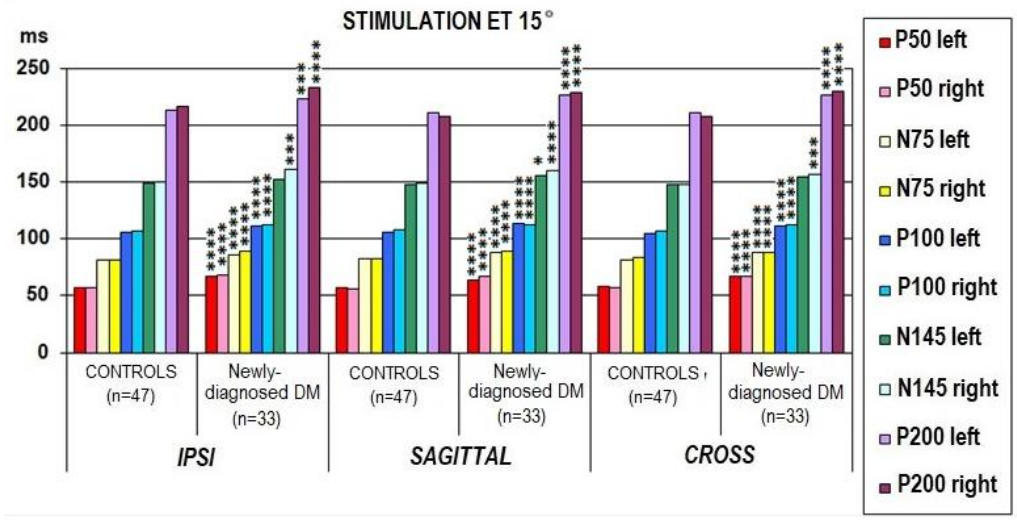
Statistical analysis was performed with IBM SPSS Statistics 23.0 statistical package. Descriptive statistical analysis was used, based on the calculation of the median and percentiles from the observed sample distribution with 95% reference interval as a limit of normal. The Refval program was used for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

Results

We performed a comparative analysis between the PVEPs values of patients with DM from each of the different groups and controls, as well as between the different groups. The examination of the known obscuration factors sex and age showed no significant difference between the study groups.

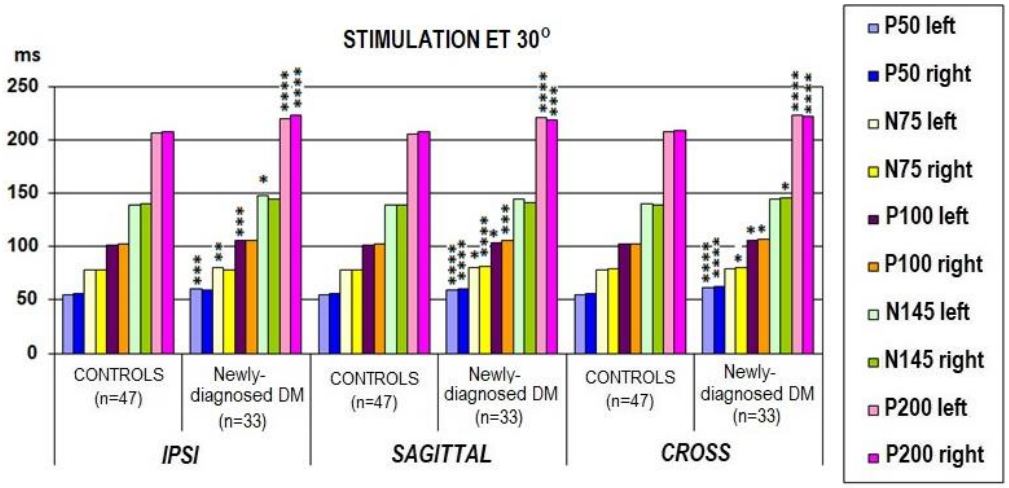
Results of the comparative analysis between PVEPs values of patients with newly-diagnosed DM without DR and controls

The patients with DM had significantly longer (in many components $p < 0.001$) L of all components in all electrode positions (EPs) at 15° and 30°, except component N145 (Figs. 1 and 2).



*p < 0.05, **p < 0.01, ***p < 0,005, ****p < 0.001

Fig. 1 Comparative analysis between PVEPs L values of patients with newly-diagnosed DM without DR and controls at 15°



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 2 Comparative analysis between PVEPs L values of patients with newly-diagnosed DM without DR and controls at 30°

In A components was found a statistically significant reduction in N75-P100 values in almost all EPs (except in sagittal), IPSI (uncrossed pathways), and CROSS (crossed pathways) at 30° right eye in patients with DM compared to controls (p < 0.01) (Table 1 and Table 2).

Results of the comparative analysis between PVEPs values of patients without DR with DM duration longer than 1 year and controls

The patients with DM had significantly longer mean L values of all components, except N145, in all EPs at 15° (p < 0.001) (Fig. 3).

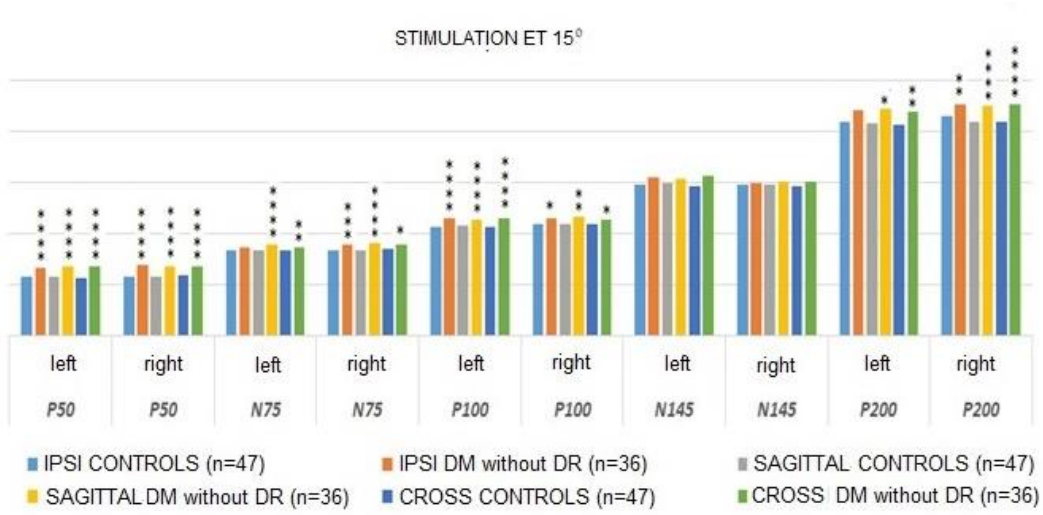
At 30° significant difference was found in P50 component only, in almost all EPs (p < 0.005) (Fig. 4).

Table 1. Comparative analysis between PVEPs A values of patients with newly-diagnosed DM without DR and controls at 15°

Electrode position	Component	Side of stim.	Stimulus	Controls (n = 47)		Newly-diagnosed DM (n = 34)		p
				$\overline{X}$	SD	$\overline{X}$	SD	
O1-Fz	N75-P100	left	15°	8.02	3.56	5.99	3.07	0.013
Oz-Fz	N75-P100	left	15°	11.41	4.90	8.78	4.53	0.016
O2-Fz	N75-P100	left	15°	8.42	3.82	6.52	3.55	0.008
O1-Fz	N75-P100	right	15°	7.85	3.80	5.76	3.01	0.014
Oz-Fz	N75-P100	right	15°	10.73	5.12	8.21	4.43	0.024
O2-Fz	N75-P100	right	15°	8.62	4.00	6.56	3.93	0.008

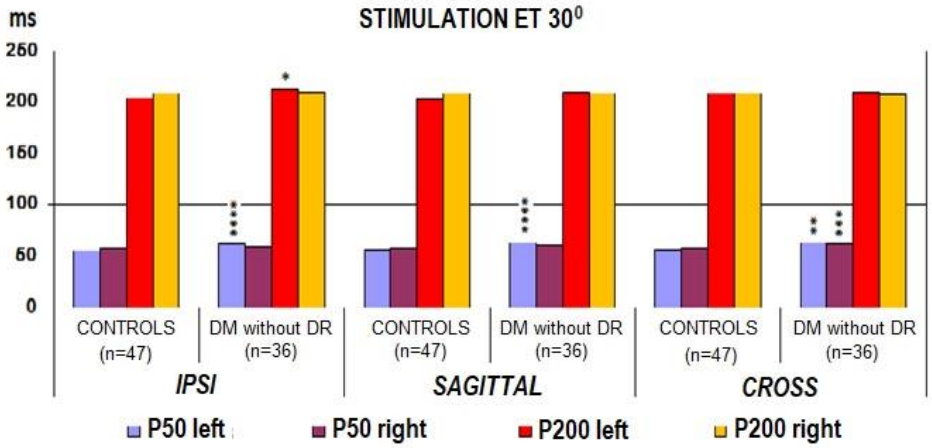
Table 2. Comparative analysis between PVEPs A values of patients with newly-diagnosed DM without DR and controls at 30°

Electrode position	Component	Side of stim.	Stimulus	Controls (n = 47)		Newly-diagnosed DM (n = 34)		p
				$\overline{X}$	SD	$\overline{X}$	SD	
O1-Fz	N75-P100	left	30°	7.20	2.76	5.24	2.00	0.002
Oz-Fz	N75-P100	left	30°	9.89	3.71	8.11	4.38	0.020
O2-Fz	N75-P100	left	30°	7.91	3.50	6.07	3.38	0.003
O1-Fz	N75-P100	right	30°	7.32	3.22	6.36	3.44	0.168
Oz-Fz	N75-P100	right	30°	10.22	4.94	8.02	3.53	0.064
O2-Fz	N75-P100	right	30°	7.88	3.49	6.96	3.54	0.186



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 3 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients without DR with DM duration longer than 1 year and controls at 15°

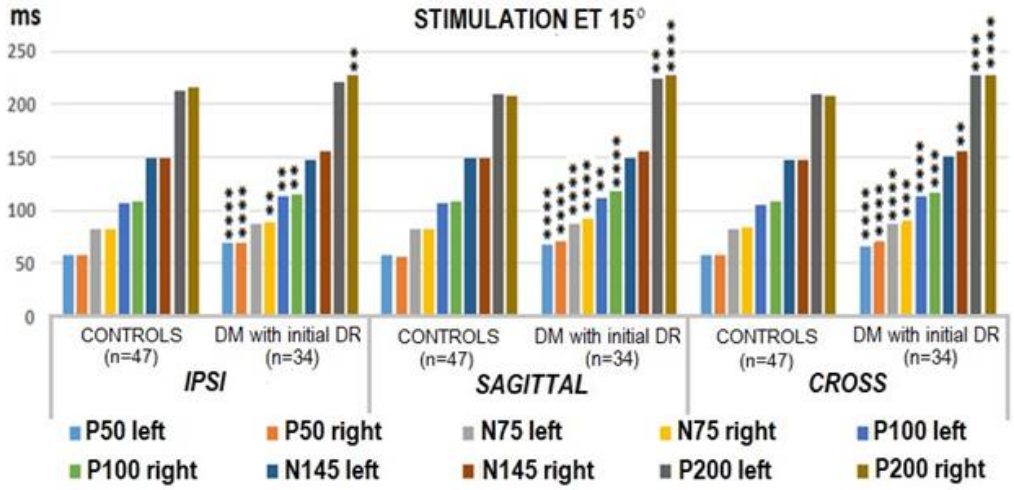


*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 4 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients without DR with DM duration longer than 1 year and controls at 30°

Results of the comparative analysis between PVEPs values of patients with DM with initial DR and controls

The patients with DM had significantly longer mean L values of all components, except N145, in all EPs at 15° (Fig. 5).

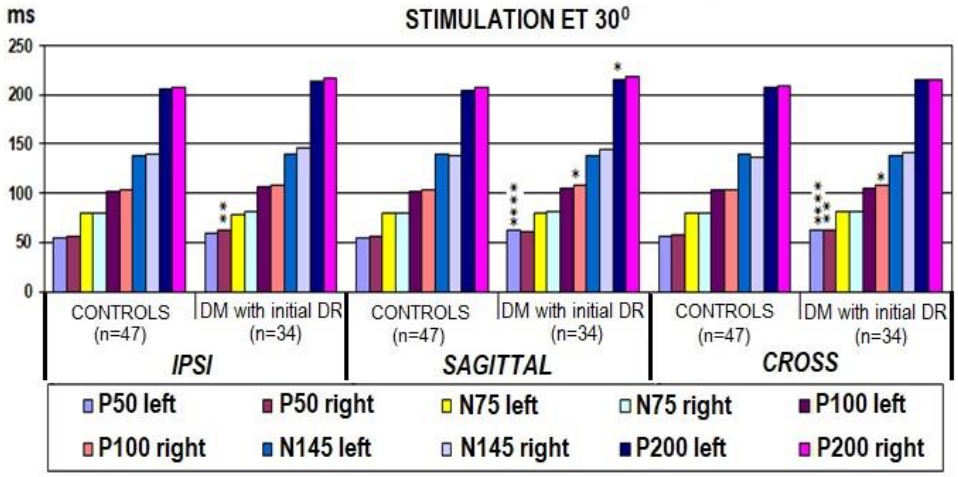


*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 5 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients with initial DR and controls at 15°

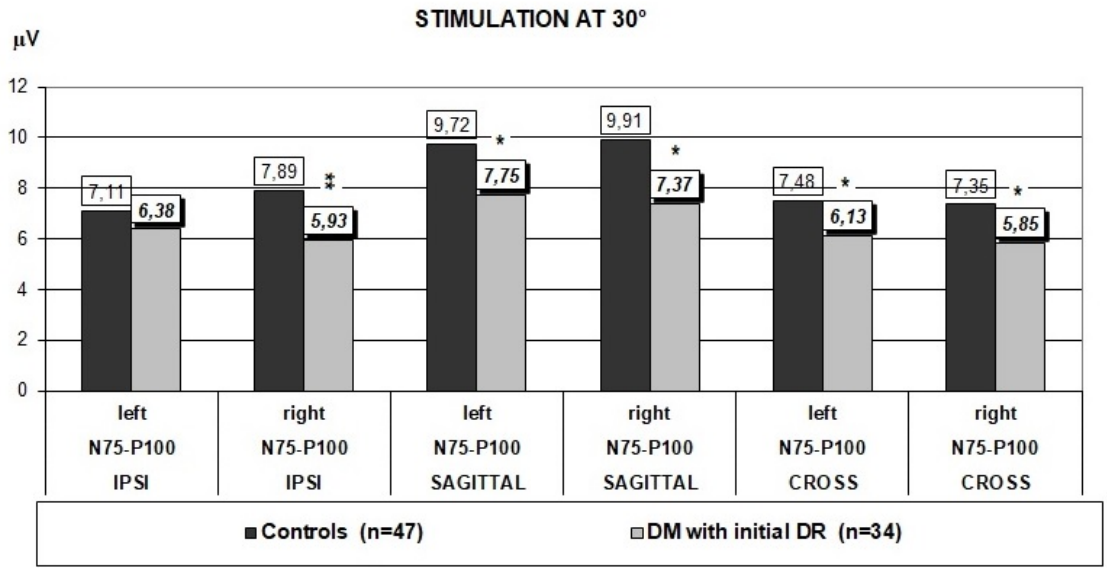
At 30° significant difference was found in P50 and P100 components only, in almost all EPs (p < 0.005) (Fig. 6).

In A components significant difference was found in N75-P100 components at 30° in all sagittal and CROSS EPs and in the IPSI EPs of right eye at 30° (Fig. 7).



$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$, $^{****}p < 0.001$

Fig. 6 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients with initial DR and controls at 30°

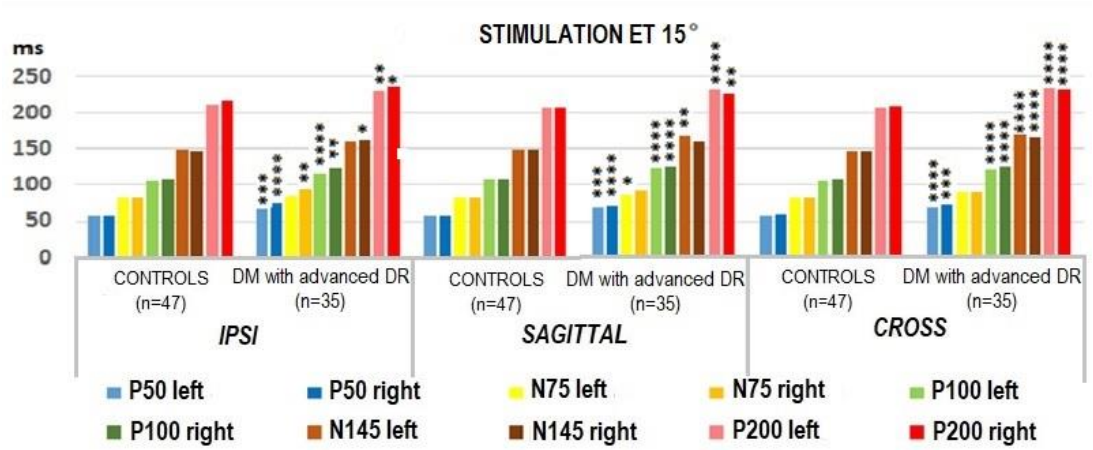


$^{*}p < 0.05$, $^{**}p < 0.01$

Fig. 7 Comparative analysis between PVEPs A values of patients with initial DR and controls at 30°

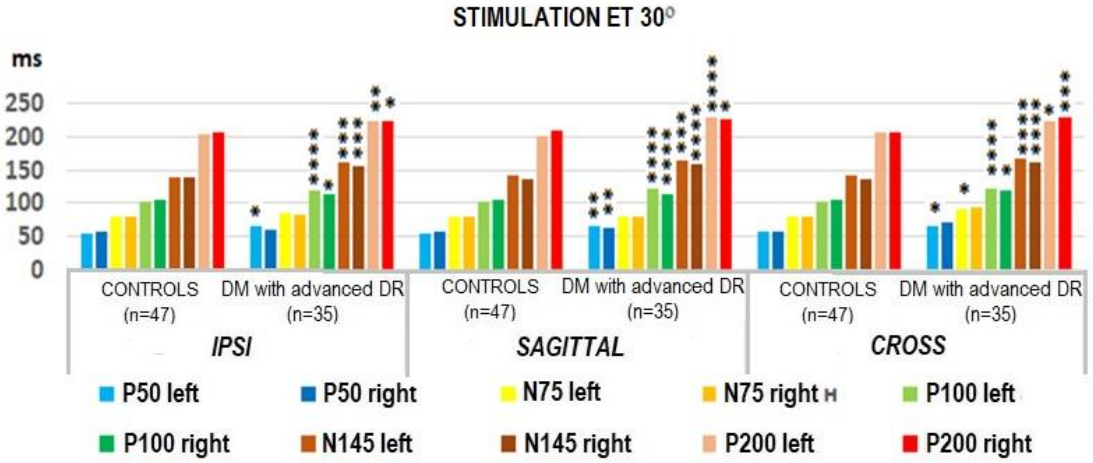
Results of the comparative analysis between PVEPs values of patients with DM with advanced DR and controls

The patients with DM had significantly longer mean L values of almost all components in all EPs at 15° and 30°, except components N75 and N145, which did not have significant difference in all EPs (Figs. 8 and 9).



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 8 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients with advanced DR and controls at 15°

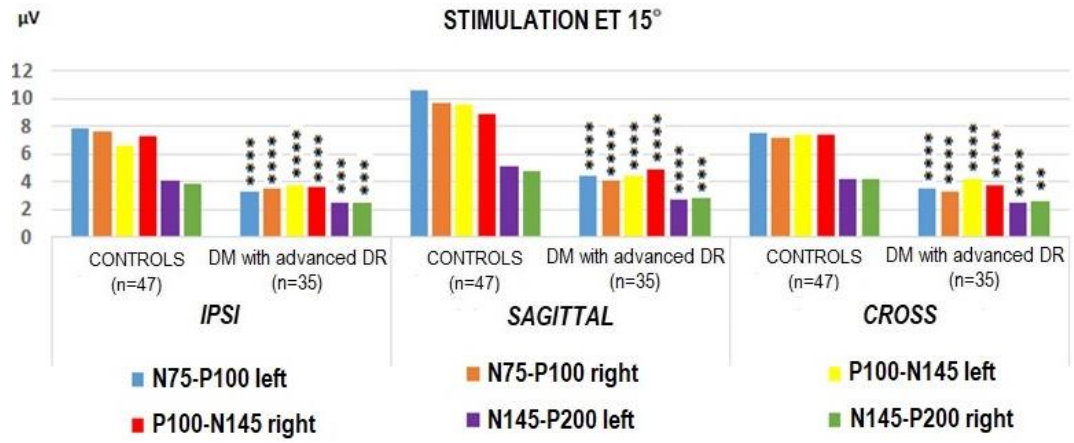


*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 9 Comparative analysis between PVEPs L values (IPSI, SAGITTAL and CROSS) of patients with advanced DR and controls at 30°

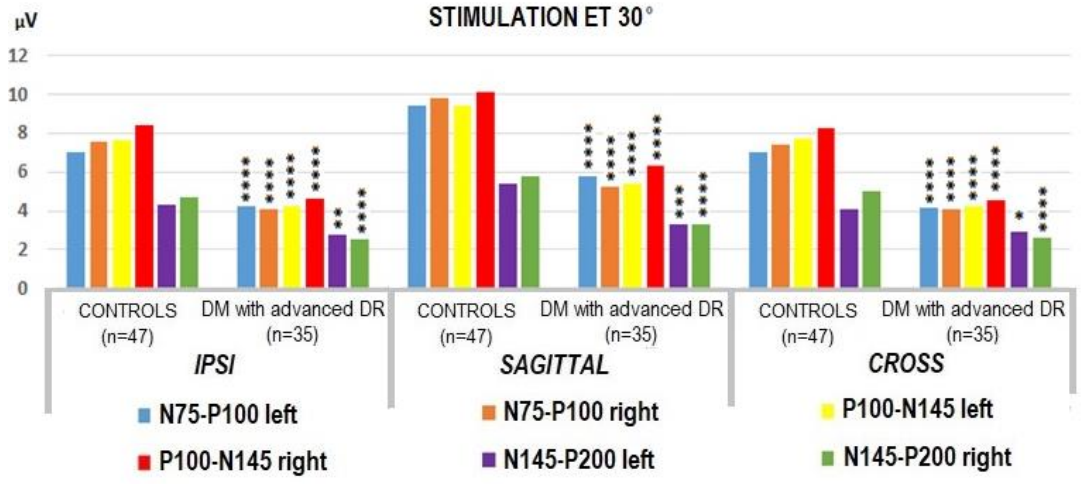
In the patients with DM all A components were significantly lower than controls in all EPs (p < 0.001) (Figs. 10 and 11).

In our study we found changes in PVEPs values in patients without DR which became more distinct in patients with initial DR group as a number of components with significant difference as well as a degree of significant difference, to reach their maximum number and significance manifestation peak in patients with advanced DR. In Fig. 12 we present the percentage distribution of the number of indicators with a significant difference from controls in the different groups. The percentage of indicators with a significant difference was 20% in the group with newly-diagnosed DM, followed by 37% in the group without DR with longer DM duration, it was increased to 60% in the initial DR group and reached 85% in the advanced DR group (Fig. 12).



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 10 Comparative analysis between PVEPs A values (IPSI, SAGITTAL and CROSS) of patients with advanced DR and controls at 15°



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001

Fig. 11 Comparative analysis between PVEPs A values (IPSI, SAGITTAL and CROSS) of patients with advanced DR and controls at 30°

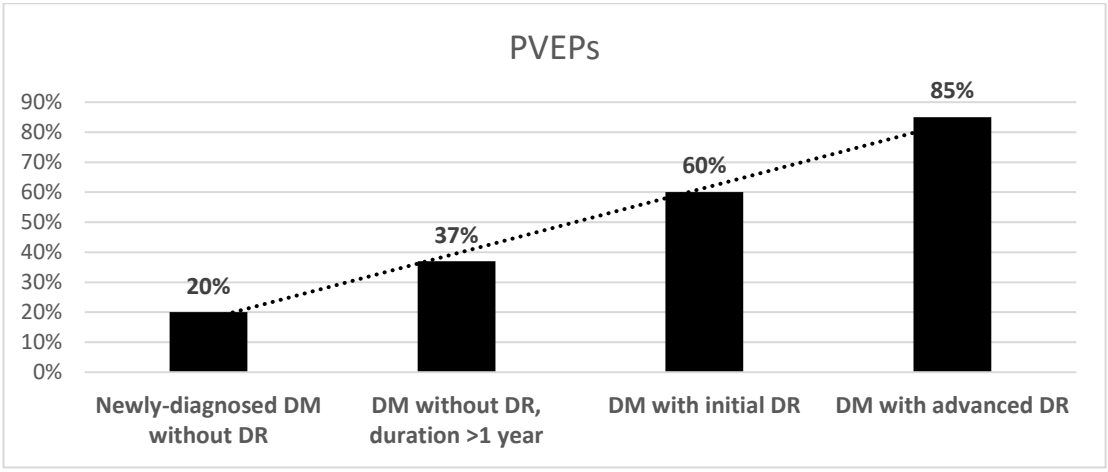


Fig. 12 Percentage distribution of the number of indicators with a significant difference from controls in the different groups

Figs. 13 and 14 clearly demonstrate the tendency of all components of PVEPs studies with advances in the retinal changes by DM – the L (meane value) was prolonged and the amplitude (mean value) was decreased at 15° and 30° in all EPs.

Fig. 13 presents the gradual elongation of PVEPs L components with the progression of the retinal changes by DM in the different groups at 15°. The same result was found at 30° also. Again, the mean P100 L component was delayed from 106.5 ms at 15° in controls to 111.8 ms in group with initial DR to reach 124.3 ms in the advanced DR group in the sagittal EPs. The same was observed for all other components at 15° and 30° for all EPs (Fig. 13).

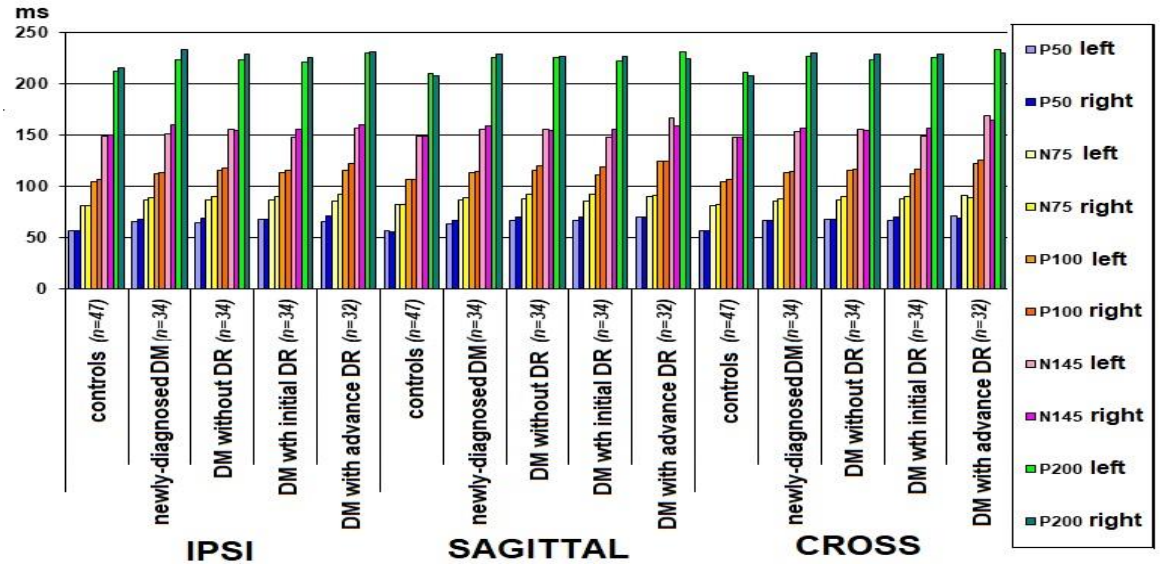


Fig. 13 Presentation of the tendency of elongation of PVEPs L with the advance of retinal changes by DR in the different groups at 15°

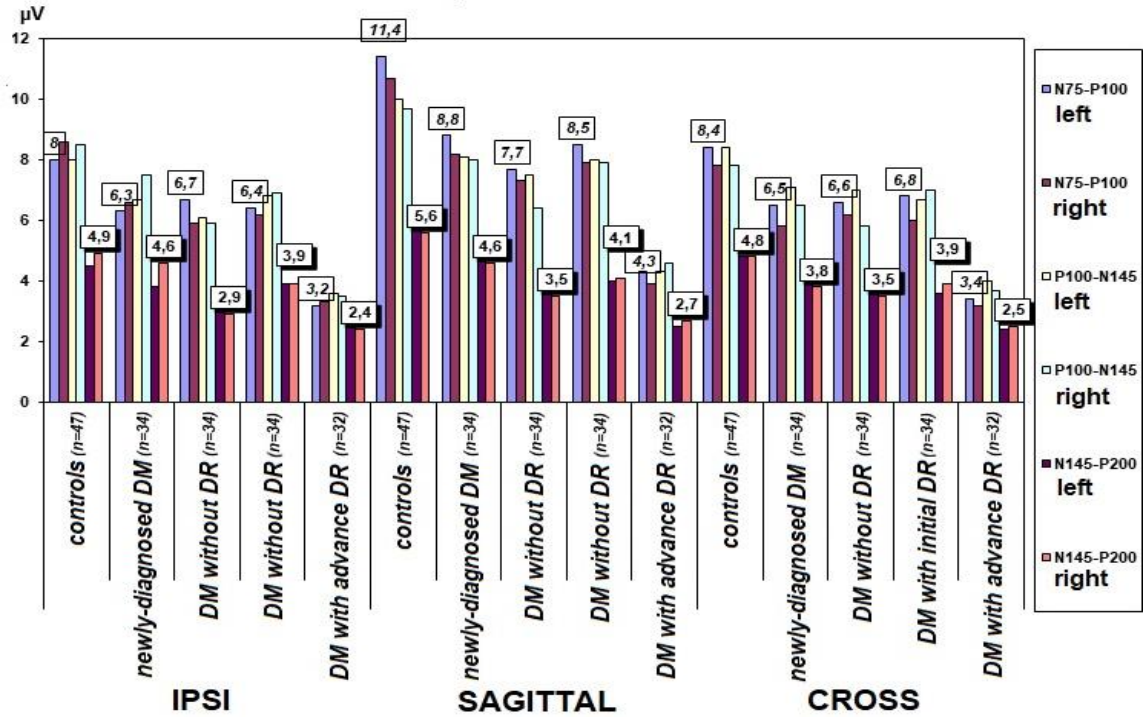


Fig. 14 Presentation of the tendency of reduction of PVEPs A with the advance of retinal changes by DR in the different groups at 15°

In A a gradual reduction in mean N75-P100 A component started from 8 μV in the control group to 6.7 μV in the group without DR and reached 3.2 μV in the advanced DR group in IPSI-EPs at 15°. The same tendency was observed in the other components at 15° and 30° in all EPs (Fig. 14).

Discussion

Our results demonstrated significant differences in most of the PVEPs components, with the most severe changes as well as the greatest number of differed indicators in the advanced DR group. We found in PVEPs statiscally significant L elongation of all components, except N145, in almost all EPs at 15° and in most of those at 30° in the diabetic patients without DR. The N75-P100 A component in PVEPs were significantly lower in some EPs at 15° in patients with newly-diagnosed DM. More sensitive were the central EPs with a greater number of significant differences found between the groups. Similar results were also described by other authors in PVEPs [12, 18]. According to [13] the peripheral stimulation tests were more sensitive.

Analysing the PVEPs results in patients with DR, we found that P50 and P100 L components were significantly longer than controls in all EPs and P200 L component was longer in the central EPs. In the advanced DR group, the L of almost all components demonstrated significant difference from controls more sensitively in the central EPs (except N75 and N145 components, which did not have a significant difference in all EPs). Authors in [21] also found no significant difference in N75 component in a group of patients with DR without being able to explain the reason. In A in the initial DR group a significant difference was observed in N75-P100 component only, but not in all EPs. In the group with advanced DR with significant difference were absolutely all A components.

We can conclude that in PVEPs the L, which is a sign of conduction changes due to local demyelinating processes, is a component that is affected earlier – first in the group of patients without DR, while the A that is a sign of axonal destruction is affected first in the group with initial DR and become the worst – with advanced retinal changes.

Such progressive changes in VEPs with the advance of diabetic retinal changes were observed in several studies available in the literature [7, 17]. A progressive PVEPs L delay, as well as reduced A, which mainly demonstrate the visual pathway changes, were described by other researchers also [1, 4, 9, 19, 24]. There are cases described in the literature, in which PVEPs were performed in patients without DR with normal VA and prolonged L was found, in most cases with reduced A also [14, 16, 23]. Authors in [11] performed a comparative study of changes in pattern electroretinography, flashERG, and PVEPs in both types of DM and found that PVEPs changes occurred earlier than PERG in both types of DM. Authors in [23] reported minor changes in ERG with significant changes in PVEPs in diabetic patients. Other authors did not detect PVEPs changes in patients without DR but only in those with DR [10].

We assume that hyperglycemia and the activation of the alternative polyol pathway of glucose metabolism cause structural changes in neurons – axonal degeneration, impaired axonal transport followed by nerve dysfunction. The accumulated around the neurons products of glycation result in segmental demyelination, disturbed axonal transport and neuronal conduction delayed. The vascular changes in vasa nervorum further increase the oxidative stress on nerve cells. PVEPs studies establish subclinical affection of the visual pathway.

Our results indicate that PVEPs could be used for early detection of changes in the VA function as a DM complication. They demonstrate that neurodegenerative changes in the VA occur very early in diabetic patients before the presence of any visible changes in the retina, indicate that the functional changes in vision in diabetic patients arise long before the structural.

Conclusion

PVEPs could be used as an objective methods for registration of early changes in the VA function as a DM complication and also to monitor the changes in dynamics as they are non-invasive, harmless, fast, not expensive and repeatable. The biggest disadvantage of these methods is their limited use in clinical practice due to the lack of equipment and the insufficient training of young doctors for their effectiveness in practice for diagnosing and monitoring the VA function in a number of ophthalmological, neurological and some systemic diseases.

Disclosures

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Conflict of interest: The author has not conflict of interest with this submission.

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