



Diabetic Retinopathy as a Neurovascular Complication with its Pre-clinical and Clinical PRVEPs Test Findings

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Abstract

Currently, diabetic retinopathy (DR) has a wide recognition as a neurovascular rather than a micro-vascular diabetic complication with an increasing need for enhanced detection approaches and preventive therapies to avoid irreversible neural damage. Pattern-reversal visual evoked potentials (PRVEPs) test as an objective electrophysiological measure of the optic nerve (ON) and retinal function can be of great value in early detection of pre-clinical DR neural changes.

Objective: The present study was designated to roll out any early PRVEPs alterations in type 2 diabetes mellitus (T2DM) patients without a clinically detected DR, and in patients with a clinically detected early non proliferative DR (NPDR). Also, to evaluate the type of these alterations that can be found.

Introduction

In the recent past, DR is frequently categorized as a micro-vascular complication of DM, however, in the last few years; DR is recognized as a neurovascular impairment or sensory neuropathy subsequent to the neurovascular impairment [1]. It is well documented that hyperglycemia and its related metabolic abnormalities have a major harmful effect on retinal neurovascular unit including neuronal, vascular, glial, and immune cells, and not just a micro-vascular effect. This hypothesis opens a new window to manage DR [2]. Many studies showed that electrophysiological procedures are sensitive tools in the early identification of diabetic neural changes way before the clinical changes become apparent on funduscopy, but its use in regular screening is still low and have obtained a much less attention than the tests for the diabetic peripheral neuropathy [3][4].

The visual evoked potentials (VEPs) test is the primary tool and is superior to the scanning procedures in assessing the functional integrity of the anterior visual pathways [5]. The PRVEPs test is a standard and an ideal modality for most clinical uses as it is less variable in timing and waveform than the other VEPs modalities, and the use of large and small size checks is recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV) standards [6], the large size (60min.) mainly stimulate the retinal neural elements responsible for peripheral vision (Para-fovea), while,

the small size (15min.) mainly stimulate the retinal neural elements responsible for central vision (Fovea) [7][8].

The most prominent component of PRVEPs wave is the P100 as a positive peak with relatively minimal variability. The increased P100 latency is an indicator for a retino-cortical conduction decrement as occur in demyelinating process, while, the P100 amplitude and waveform abnormalities may indicate axons loss in the visual pathway [9].

The aim of this study was to clarify the usefulness of PRVEPs test to detect the early diabetic impact on the ocular neural elements before any overt DR clinical changes and the extent of this impact on a clinically documented early NPDR. Also, to evaluate the type of this impact.

2. Subjects and Methods:

2.1. Study Design:

This is a case-control study carried out in Basrah governorate, Iraq, from December 2017 to November 2018. The study included 138 subjects who attended the ophthalmology consultant unit in Alkawanaa teaching hospital. The subjects were divided into group (A) which included 50 patients with T2DM and did not have a clinically detected DR, group (B) which included 38 patients with T2DM and had a clinically detected mild-moderate NPDR [10], and the control group which included 50 subjects who were neither diabetic nor have any medical or ophthalmic condition that might affect PRVEPs test results.

The PRVEPs were recorded using the RETI-port/scan 21 machine (Roland Consult, Brandenburg/Havel, Germany). And done according to ISCEV standards [6], by using a full field pattern of black and white checks with central red fixation point, the checkerboard stimulus was of two sizes, a large (60min.) and a small (15min.) size checks. Monocular recording of both eyes done by using a single channel electrodes of gold plated type, with a four channel amplifier which its band-pass filters were set at (1-50Hz). The contrast was 97%, the plot time was (300msec.), and the stimulus frequency was (1.53872 reversal per second). These test parameters were customized by the manufacturer and designated to measure the latency of N75, latency and amplitude of P100.

2.2. Exclusion Criteria:

Significant ocular diseases as sever NPDR, PDR, macular disease, vitreous opacities, visually significant cataract, glaucoma, ON disease, best corrected visual acuity less than 6/6, and amblyopia. Any medical illness that can affect PRVEPs findings as multiple sclerosis (MS), Epilepsy, hypothyroidism, T1DM, patients with past history of head trauma or cerebrovascular accident (CVA), and un controlled hypertension in which blood pressure (BP) above 140/90 mmHg. Alcoholic and drug addict as heroin, morphine, cough syrups, pain

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Received: July 02, 2020 Accepted: July 11, 2020 Published: July 29, 2020

killers and sedatives due to they have a negative impact on neural transmission [11]. Pregnant women.

2.3. Data Collecting:

Each candidates underwent a thorough history, BP, weight, height and fasting plasma glucose (FPG) measurement, and a comprehensive ophthalmic examination including refraction and visual acuity, intraocular pressure (IOP), anterior and fundus segment examinations after mydriasis.

2.4. Subjects and Testing Room Preparation:

A verbal consents were taken from all subjects who had a briefing about the procedure and instructed to fast the night before the tests, and to avoid hair oils and cycloplegic drops. Subjects were seated comfortably in a stable position approximately 100cm away from the monitoring screen and the tested eye was in a proper alignment to the central fixation point with a precise focusing on it during testing. Subjects with refractive errors were asked to wear their corrective glasses. The testing room was kept quit and dim lighted with no other operating instruments during the test.

2.5. Electrodes Placement:

Done according to the International 10/20 system [6], [7], by gently scrubbing the scalp sites by a piece of cotton and skin preparation gel, then the electrode paste was applied inside the electrodes to slightly overflow it, the electrodes placed with the active electrode at the occipital scalp (Oz), the reference electrode at the frontal scalp (Fz) and grounded at the vertex (Cz). the electrode impedance was checked and kept ≤ 5kohm and the impedance difference among electrodes was ≤ 3kohm.

2.6. Statistical Analysis:

The data were analyzed by using SPSS version 20. One-way (ANOVA) test was used to test the significant differences between the three groups. Significant differences between each paired groups were then evaluated by Post Hoc Tukey test, and the P-value < 0.05 was considered as the lowest limit for significance.

3. Results:

The baseline characteristic of the cases and controls were presented in Table (1). Both right and left eye of the controls and group A were included, while only the eyes which submitted the clinical features of mild-moderate NPDR [10] and were able to visualize the central red fixation point in both tests, were included as group B.

Table (1):The baseline characteristics among cases and controls (Mean ± SD)

Variables	Controls N=60	Group A N=60	Group B N=38
Age	(55.4 ± 7.4)	(58.5 ± 6)	(60.2 ± 7)
Sex (male/female)	25/35	26/34	19/19
BP (mmHg)	Systole (125.3 ± 11.3)	(122.8 ± 10.8)	(123 ± 9.8)
	Diastole (78.5 ± 8.3)	(77.2 ± 9.2)	(79.6 ± 8)
BMI (kg/m ²)	(30.7 ± 3.4)	(29.4 ± 3.3)	(29.1 ± 3.0)
FBS (mg/dl)	(88.6 ± 9.5)	(103.8 ± 33.8)	(178.4 ± 34.4)
Tested Eyes right/left	30/30	30/30	37/38

The tests results of both eyes will be submitted to gather without right\left discrimination as there was no statistically significant difference in the mean values of the three parameters of both PRVEPs tests between the right and left eyes of each group. Table 2 and 3 presented the 60min. and 15min. PRVEPs tests results respectively of both eyes in each group.

Table (2): The 60min. PRVEPs test results of both eyes in each group (mean ± SD)

60min. PRVEPs test parameters	Control N=100 eyes	Group A N=100 eyes	Group B N=78 eyes	LSD
N75 Latency (ms)	68.3 ± 6.7	69.4 ± 6.7	71.3 ± 8.4	NS
P100 Latency (ms)	104.37 ± 4	108.61 ± 1.8	117.5 ± 8	4.81
P100 Amplitude (µV)	12.6 ± 3.05	10.4 ± 4.7	8.2 ± 4.84	2.14

Different letters represent significant difference at (P-Value < 0.05).

Table (3): The 15min. PRVEPs test results of both eyes in each group (mean ± SD)

15min. PRVEPs test parameters	Control N=100 eyes	Group A N=100 eyes	Group B N=78 eyes	LSD
N75 Latency (ms)	82.37 ± 6.01	81.8 ± 11	79.8 ± 11.6	NS
P100 Latency (ms)	110.4 ± 3.5	121.5 ± 5.8	127.2 ± 4	3.7
P100 Amplitude (µV)	15.55 ± 7.87	11 ± 3.61	7.7 ± 4.8	3.03

Different letters represent significant difference at (P-Value < 0.05).

The data in both Tables (2) and (3) revealed that in both tests, there was an increase in the mean values of P100 latency significantly and a decrease in the mean values of P100 amplitude significantly in group B as compared to group A and controls, and the differences among group A and controls were also significant. With regard to N75 latency mean value, no statistical significant difference was detected among the three studied groups as P-value was more than 0.05.

As the N75 latency mean values were of comparable results with no significant difference in both PRVEPs tests. So that, the P100 components seemed to be a more reliable parameters to estimate the proportion of the abnormal PRVEPs test results in each group in relation to the controls means of this study. By calculating the upper limit of the normal P100 latency for the 60min. test (110.32) and for 15min. test (115.9), while, the lower limit for normal P100 amplitude for the 60min. test (7.55) and for 15min. test (7.98), to use them as the cutoff point between normal and abnormal results. The proportions of normal and abnormal 60min. and 15min. test results are shown in Tables (4) and (5) respectively.

Table (4): The proportion of normal and abnormal 60min. test results

60min. PRVEPs test	Control	Group A	Group B
P100 latency	normal	82%	64%
	abnormal	18%	36%
P100 amplitude	normal	60%	46%
	abnormal	40%	54%

Table (4) presented that the proportion of abnormal P100 latency is higher than the proportion of abnormal P100 amplitude in group B, while the proportion of abnormal P100 latency and amplitude in group A were comparable. And in the controls. only 18% and 40% gave abnormality in P100 latency and amplitude respectively.

Table (5): The proportion of normal and abnormal 15min. test results

PRVEPs test	Control	Group A	Group B
P100 latency	normal 52%	15%	3%
P100 latency	abnormal 48%	85%	97%
P100 amplitude	normal 90%	89%	38%
P100 amplitude	abnormal 10%	11%	62%

Table (5) indicated that the proportion of abnormal P100 latency is higher than the proportion of abnormal P100 amplitude in group A and B, while the abnormal proportions P100 latency and amplitude in controls were comparable.

4. Discussion:

Although, the main clinical diagnosis of DR is based on subjective detection of micro-vascular changes, functional test as electrophysiological measures have the potential to be an alternative determinants [12]. According to Hari Kumar KVS. et al [13] the VEPs changes were evident even in the short-term high blood glucose in gestational DM and T2DM pregnant females in comparison to normal glycemic pregnant females in spite of all being free from DR.

In the present study, both tests results of group A revealed a statistically significant delay in the mean value of P100 latency and a decrease in the mean value of P100 amplitude when compared with the controls P100 latency and amplitude respectively, and these results were in accordance with Gupta S. et al [14] for the 60min. test and with Heravian J. et al [15] for the 15min. test. In addition, the presence of clinical findings of early NPDR in group B associated with a more prolongation in the P100 latency and a more decrease in the P100 amplitude in comparison to controls and group A, these results were in accordance with other studies results [15], [16]. These indicated that the PRVEPs test parameters are deranged in diabetic patients prior to the development of a clinically significant DR and is more deranged with the presence of DR. While, Daniel R. et al [17] who used mid-size checks (24-32min.), detected a significant delay in P100 latency, but no significant decrease in P100 amplitude. This may be attributed to factors affecting the P100 amplitude as it is more influenced by technical factors and subject cooperation than the P100 latency [7].

In both tests results of group B, the proportion of abnormal P100 latency were higher than that of P100 amplitude with a higher abnormal proportions in 15min. test, suggesting that the P100 latency affected more in the presence of early NPDR features. Whereas in group A, only the 15min. test showed a higher proportion of abnormal P100 latency than that of P100 amplitude, and also higher than that of the 60min. test which revealed that the P100 latency and amplitude affected almost equally. this might indicate that the P100 latency of 15min. PRVEPs test is a significant indicator to the presence of neural damage before the development of DR clinical feature. These proportions were greater than that measured in other studies [15], [16]. This variability could be explained by variation in the inclusion and exclusion criteria, DR diagnosis, stimulus recording conditions and parameters. And as the proportions of abnormal P100 latency for group A and group B in 15min. test were higher than that of 60min. test. this could suggest that the central vision is affected much earlier and more altered with the presence of DM and DR changes than the peripheral vision.

In the 15min. test results demonstrated that the delay in P100 latency affected more than the decrease in P100 amplitude in group A and this mainly resembles the MS features. Thus, early diabetic ocular involvement seem to be a conductive damage at the myelin sheath

level of ON fibers [15]. And in group B, the presence of early NPDR clinical features was associated with a more delay in the P100 latency and a more decrease in P100 amplitude and these results also follow the VEPs changes in MS patients, in which the VEPs progressively delayed and then as demyelination progresses, the amplitude will be attenuated [5].

The changes in myelin sheath of ON is stated for the first time in experimental diabetes by Fernandez DC et al [18], who identified extensive myelin irregularities and axonal loss with oligodendrocyte and astrocyte abnormalities at the distal portion of the ON and all were preceding retinal ganglion cell loss, these changes were detectable in animal models after only six weeks of diabetes. More recently, the reactive gliosis and neuronal apoptosis are hypothesized as an early DR processes, and these imply DR as a neurovascular complication [19]. These neural alterations were also detected anatomically by using spectral domain optical coherence topography in many studies which frequently reported thinning in the retinal nerve fiber layer and inner plexiform layer of diabetic patients with minimal or no DR as in [20], [21].

Comparing with other diabetic neuropathy, it seem to follow same path as in polyneuropathy of peripheral nerves, as Valls-Canals J. et al [22] concluded that the diabetic polyneuropathy is of two kinds: a demyelination which occur with and without symptoms, and an axonal loss which is the main cause of symptoms. The DR pathology seems to be an actual central neuropathy similar to that of the peripheral nerves [3].

The perception of neural alterations as an early stage of DR proposes the possibility to find out other treatment to prevent vision loss [23]. In the nearest future, it is very likely that DR management will be established on neuroprotective agents [24]. And the PRVEPs tests seem to be a good utility to explore the efficacy of these new approaches.

5. Conclusions:

Collectively, the results of PRVEPs tests in this study are highly confirmative to the presence of neural alteration in the retina and ON before any clinically diagnosed DR, mainly in form of conductive defect. In addition, these tests are non-invasive, quick, objective, cheap, and not require mydriasis. Therefore, PRVEPs tests should be considered as a valid tool for screening and follow up of diabetic patient to detect any early preclinical changes of DR which could be of great value in prevention of permanent neuronal loss and blindness. In addition, the results of 60min. test were not the same as the results of 15min. test in both patients groups, these could indicate that the T2DM effect on the different part of the retina is not similar with a more impact on the central vision.

Recommendations:

Further studies are required with the simultaneous use of pattern electroretinogram (PERG) and PRVEPs tests, to distinguish between the purely ON changes from that of retinal abnormality origin.

6. References:

1. Stem MS, Gardner TW. Neurodegeneration in the Pathogenesis of Diabetic Retinopathy: Molecular Mechanisms and Therapeutic Implications. *Current Medicinal Chemistry*. 2013;20:3241-3250.
2. Duh EJ, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *Journal of Clinical Investigation Insight*. 2017;2:1-13.
3. Pescosolido N, Barbato A, Stefanucci A, Buomprisco G. Role of

- Electrophysiology in the Early Diagnosis and Follow-Up of Diabetic Retinopathy. *Journal of Diabetes Research*. 2015;2015:319692.
4. Deák K, Fejes I, Janáky M, Várkonyi T, Benedek G, Braunitzer G. Further Evidence for the Utility of Electrophysiological Methods for the Detection of Subclinical Stage Retinal and Optic Nerve Involvement in Diabetes. *Medical Principles and Practice*. 2016;25:282-285.
 5. Creel D. Visually Evoked Potentials. In: Kolb H, Fernandez E, Nelson R, editors. *Webvision: The Organization of the Retina and Visual System*. Salt Lake City (UT): University of Utah Health Sciences Center Copyright: (c) 2018 Webvision.; 1995.
 6. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, et al. ISCEV standard for clinical visual evoked potentials: (2016 update). *Documenta Ophthalmologica Advances in ophthalmology*. 2016;133:1-9.
 7. Epstein C. M. et al. American Clinical Neurophysiology Society Guideline 9B: Guidelines on visual evoked potentials. *Journal of Clinical Neurophysiology: official publication of the American Electroencephalographic Society*. 2006;23:138-156. Available at (<https://www.acns.org/practice/guidelines>).
 8. Holder GE, Celesia GG, Miyake Y, Tobimatsu S, Weleber RG. International Federation of Clinical Neurophysiology: Recommendations for visual system testing. *Clinical Neurophysiology*. 2010;121:1393-1409.
 9. Walsh P, Kane N, Butler S. The clinical role of evoked potentials. *Journal of Neurology, Neurosurgery & Psychiatry*. 2005;76:ii16.
 10. Wilkinson CP, Ferris FL, III, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110:1677-1682.
 11. Garg S, Sharma R, Thapar S, Mittal S. Visual Evoked Potential Response Among Drug Abusers- A Cross Sectional Study. *Journal of Clinical and Diagnostic Research : JCDR*. 2016;10:CC23-CC26.
 12. Nasrallah Z, Robinson W, Jackson G, Barber AJ. Measuring visual function in diabetic retinopathy: progress in basic and clinical research. *Journal of Clinical Experimental Ophthalmology*. 2013;4:4-11.
 13. Hari Kumar KVS, Ahmad FMH, Sood S, Mansingh S. Visual Evoked Potential to Assess Retinopathy in Gestational Diabetes Mellitus. *Canadian Journal of Diabetes*. 2016;40:131-134.
 14. Gupta S, Gupta G, Deshpande VK. Visual evoked potential changes in patients with diabetes mellitus without retinopathy. *International Journal of Research in Medical Sciences*. 2015;3:3591-3598.
 15. Heravian J, Ehyaei A, Shoeibi N, Azimi A, Ostadi-Moghaddam H, Yekta A-A, et al. Pattern visual evoked potentials in patients with type II diabetes mellitus. *Journal of Ophthalmic & Vision Research*. 2012;7:225-230.
 16. Kothari R, Bokariya P, Singh S, TS H. Evaluation Of The Role Of Visual Evoked Potentials In Detecting Visual Impairment In Type II Diabetes Mellitus. *DJO Delhi Journal of Ophthalmology*. 2018;28:29-35.
 17. Daniel R, Ayyavoo S, Dass B. Study of visual evoked potentials in patients with type 2 diabetes mellitus and diabetic retinopathy. *National Journal of Physiology, Pharmacy and Pharmacology*. 2017;7:159-164.
 18. Fernandez DC, Pasquini LA, Dorfman D, Aldana Marcos HJ, Rosenstein RE. Early Distal Axonopathy of the Visual Pathway in Experimental Diabetes. *The American journal of pathology*. 2012;180:303-313.
 19. Araszkievicz A, Zozulinska-Ziolkiewicz D. Retinal Neurodegeneration in the Course of Diabetes-Pathogenesis and Clinical Perspective. *Curr Neuropharmacol*. 2016;14:805-809.
 20. Pekel E, Tufaner G, Kaya H, Kaşıkçı A, Deda G, Pekel G. Assessment of optic disc and ganglion cell layer in diabetes mellitus type 2. *Medicine*. 2017;96:e7556.
 21. Dhasmana R, Sah S, Gupta N. Study of Retinal Nerve Fibre Layer Thickness in Patients with Diabetes Mellitus Using Fourier Domain Optical Coherence Tomography. *Journal of Clinical and Diagnostic Research : JCDR*. 2016;10:NC05-NC9.
 22. Valls-Canals J, Povedano M, Montero J, Pradas J. Diabetic polyneuropathy. Axonal or demyelinating?. *Electromyography and clinical neurophysiology*. 2002;42:3-6.
 23. Barber AJ, Baccouche B. Neurodegeneration in diabetic retinopathy: Potential for novel therapies. *Vision research*. 2017;139:82-92.
 24. Mrugacz M, Bryl A, Bossowski A. Neuroretinal Apoptosis as a Vascular Dysfunction in Diabetic Patients. *Curr Neuropharmacol*. 2016;14:826-830.

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