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Research Article

Visual evoked potential changes in patients with diabetes mellitus without retinopathy

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder, associated with a great deal of morbidity in the patients due its chronic complications including diabetic retinopathy. Visual evoked potentials (VEPs), which assess the functional integrity of the visual functions from retina to visual cortex, can prove to be a sensitive tool to study the possible effects that diabetes may exert on the visual system. In patients without clinically evident retinopathy, electrophysiological evidence of visual dysfunction can help in early detection of the visual involvement. Hence, this study attempted to detect the presence of such visual dysfunctions in the diabetics without retinopathy by pattern-reversal visual evoked potentials (PRVEPs).
Methods: PRVEP was recorded in 116 subjects (64 diabetics without retinopathy and 52 controls). P100 latency, N75-P100 amplitude and interocular latency differences were compared between the diabetics and the controls. The parameters were compared among the groups with different duration of the disease as well as those with different glycaemic status.
Results: The study has demonstrated significant prolongation of mean P100 latency, reduction in N75-P100 amplitudes and increased interocular latency difference in the diabetics as compared to the control group. The duration of the illness was found to alter the mean P100 latency while the glycaemic status of the diabetics was not found to be correlated with the PRVEP abnormalities.
Conclusions: VEP responses are deranged in diabetic patients before the development of retinopathy. VEP measurements can be used for the early diagnosis of visual dysfunctions in the diabetes for a better prognosis of the condition.

Keywords: Diabetes mellitus, Visual evoked potentials

INTRODUCTION

Diabetes mellitus continues to be a major clinical challenge in India and is rapidly gaining the status of a potential epidemic in the country with more than 62 million diabetic patients.[1] It has become a major public health burden with adult-onset blindness, end-stage renal disease and non-traumatic limb amputation. Urbanization leading to lifestyle changes, obesity and insulin resistance are the risk factors peculiar for developing diabetes among Indians.[1]

Among the group of chronic complications, detecting the neurological complications assume great importance as these have been found to be causing a great deal of morbidity in diabetic patients. Diabetic retinopathy is the sixth cause of blindness in the country from being the 17th cause of blindness 20 years ago with 18% of diabetics above 40 years having diabetic retinopathy.[2] It has become a leading cause of blindness despite the fact that visual loss due to DM (Diabetes-mellitus) may be prevented by glycaemic control or photocoagulation.[3-6] Unfortunately, it is too late for effective treatment in many cases as the patient remains asymptomatic till progression. After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment.[7]

Diabetic neuropathy is another chronic complication involving damage to the nerves and affects upto 50% of people with diabetes and is clearly related to the presence, duration and severity of hyperglycemia. In contrast to pathological studies, electrophysiological investigation is a very sensitive method in determining peripheral and central neuropathy in diabetic patients. Extensive electrophysiological documentation exists for the occurrence of peripheral neuropathy during the course of diabetes. Growing attention has been focused on a more general involvement of the nervous system in diabetes, affecting not only, the peripheral but also, more interestingly the central nervous system. As for many years, the electroencephalography was the only technique available for the study of electrical activity of the human cerebral cortex, the information provided was limited, particularly in the assessment of deeper brain structures.8 Advanced electro-physiological techniques to assess the cerebral function, such as the measurement of evoked potentials like the visual evoked potentials (VEPs), have increased our understanding of the normal visual functions.[8] Evoked potentials have evolved from a challenging scientific tool to a commonly applied technique in clinical neurology and central neural conduction can be evaluated by clinical use of the evoked potentials. Visual evoked potentials record the electrical potential differences from the scalp in response to visual stimuli and can provide important diagnostic information regarding the functional integrity of the visual system. These are objective and non-invasive methods of investigating the visual system. Pattern VEP is the preferred technique for most clinical purposes, the results of which are less variable in waveform and timing than the results elicited by other stimuli.[9] As VEP examination, with the analysis of the P100 wave, assesses the visual function from retina to the visual cortex, it can prove to be a sensitive tool to study the possible effects that diabetes may exert on the visual system. Moreover, VEP abnormalities arise before diabetic retinopathy signs become clinically detectable hence, anomalies that occur long before clinically evident structural alterations in the retina and in visual pathways, can be detected by this objective and non-invasive electrophysiological technique.[10] The present study hence attempt to detect the subclinical involvement of visual functions in diabetes by pattern-reversal visual evoked potentials (PRVEP) and to assess the value of the test in detecting pre-clinical form of diabetic retinopathy which could contribute greatly to the prevention of diabetic retinopathy complications.

METHODS

A cross-sectional comparative study was conducted on 116 subjects. Out of 116 subjects, 64 subjects were diabetics who were newly diagnosed patients of diabetes mellitus attending the Department of Medicine in Acharya Vinoba-Bhave Rural Hospital (A. V. B. R. H.) Sawangi (Meghe), Wardha, Maharashtra, India and 52 subjects were age and sex-matched healthy volunteers from the area of study (students and staff of Jawaharlal Nehru medical college, Sawangi (Meghe), Wardha, Maharashtra, India. The test was conducted in the Neurophysiology laboratory in the department of Physiology.

Inclusion criteria

All patients with diabetes mellitus either type 1 or type 2, (proven by recent blood glucose studies with fasting blood glucose estimated prior to recording of VEP) with normal visual acuity or corrected by glasses and normal fundus examination.

Exclusion criteria

All the patients with cataract, glaucoma, vitreous opacities or any evidence of optic atrophy, diabetic retinopathy, patients with long standing hypertension as evidenced by fundus appearances and ECG as well as clinical examination, patients with past history of cerebro-vascular accidents, chronic alcoholics, patients with peripheral nervous system disorders unrelated to diabetes.

The sample-size was decided on the basis of review of data of the Department of Medicine of the hospital for the number of newly diagnosed diabetic patients in the department presenting every month and hence, number of patients for the study period (30 months) was estimated accordingly. The sample size calculation provided 90 diabetics for the study. After fulfilling the case definition (proven cases of diabetes mellitus, type 1 or type 2 as per the WHO criteria) and obtaining informed consent, 90 patients were enrolled through simple random-sampling method. Of 90 patients, 64 patients were included in the study group as 16 patients were with diabetic retinopathy, 5 had long standing hypertension and 2 patients were chronic alcoholics (exclusion criteria in the study) and 3 patients exhibited non-compliance. Approval from the Institutional Ethical committee was obtained for the study.

Patients were grouped in 3 categories, based on the fasting blood sugar levels as: Good control (80-120 mg

%), Fair control (121-140 mg %) and Poor control (>140 mg %). Another classification was on the basis of the duration of diabetes with group 1 (<5 years), group 2 (6-10 years) and group 3 (>10 years). Every case included in the study was examined in details with careful neurological examinations after taking a detailed clinical history. Written informed consent was obtained before the test.

Pretest evaluation

For the best results of VEP testing, subjects were advised to come without applying oil or any hair chemical to the scalp, asked to put on their usual glasses. Subjects were instructed to have an adequate sleep the previous night to prevent the effect of drowsiness on the responses. Subjects were explained about the test to ensure full cooperation. They were also instructed to avoid any mydriatic or miotic drug 12 hours before the test. Preparation of scalp skin was done before electrode application.

VEP Recording

VEP was performed on RMS Polyrite-Ad, a specially equipped electro-diagnostic procedure room, made dark and sound attenuated for the test. Subjects were seated comfortably about 95 cm away from a video-monitor with a 30 cm screen. The video- monitor presented a black and white checker-board pattern with a fixation spot in the centre of the screen (mean luminance 50 candela/m^2 and contrast 70%). The checks/pattern elements reversed alternately at the rate of 1.71 Hz. The visual angle subtended by the checks was 54.6 min and the screen subtended a visual angle of 19 degrees. The signals were amplified (gain 20,000), filtered with a system band pass filter of 2-200 Hz and 100 responses were averaged. Standard disc surface electrodes were placed according to the International 10/20 system of electrode placement, with active electrode at Oz, reference electrode at Fz and ground electrode at Fpz. 11 Volunteers were instructed to fix the gaze on a small red square at the Centre of the screen of video-monitor. Monocular stimulation was done with an eye-patch covering the other eye. With the preset stimulus and recording conditions as mentioned above and keeping the electrode impedance <5 kΩ, the recording procedure was started. To verify the reproducibility of the waveform, two responses were recorded and superimposed. The replicated response measurements with P100 latency within 2.5 ms difference and N75-P100 (peak-peak) amplitude within a 15% difference was accepted.[11]

The Parameters for the study were Peak P100 latencies, N75-P100 amplitudes and interocular latency-difference. All the data was expressed as mean ±S.D. The significance of difference between groups was calculated by using Z-test, one way ANOVA and Tukey multiple comparison tests.

Statistical analysis was done by using SPSS (Statistical package for social science) version 14.0 and Grafpad (Prism 4) statistical software's. The analysis was done at 5% level of significance.

RESULTS

The study group comprised of 64 diabetics with majority (62.5%) in the age group of 41-60 years. 57.8% of the diabetics were in the group with <5 years of duration of diabetes as in Figure 1. The study group consisted of both Type 1 (6.25%) and Type 2 diabetics (93.75%). Type 2 cases exhibited poorer control of glycaemic status with mean fasting blood sugar of 167.76 mg/dl while those with Type 1 diabetes had mean fasting blood sugar (FBS) level of 139.25 mg/dl. The mean fasting blood sugar level in the total test group was 165.98 mg/dl as in Figure 2. Classification on the basis of their glycaemic status revealed a mean fasting blood sugar of 102.85 mg/dl with good metabolic control, with fair control group as 134.61 mg/dl and with poor control; it was 191.79 mg/dl as in Figure 3.

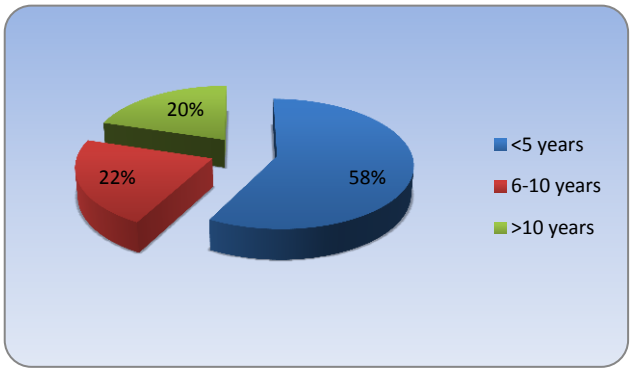


Figure 1: Distribution of patients according to the duration of diabetes.

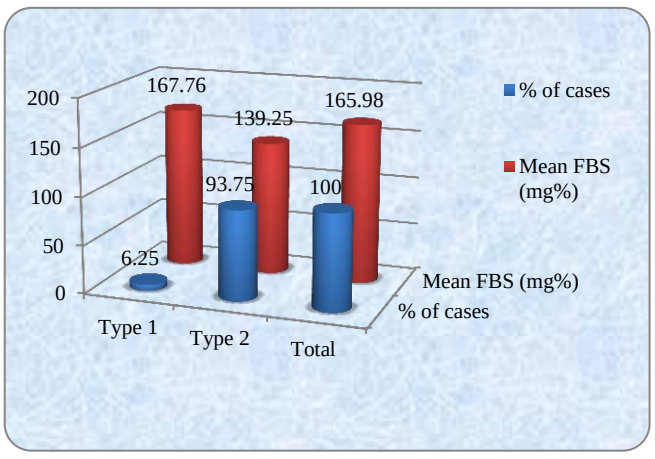


Figure 2: Mean fasting blood sugar (FBS) levels in Type 1 and Type 2 diabetics.

PRVEP was recorded in the study as well as the control group and P100 latency, N75-P100 amplitude and interocular latency differences were analysed (Figure 4). Mean values of PRVEP parameters (P100 latency and N75-P100 amplitude) were obtained for both right and left eyes in all the 116 subjects (64 diabetics and 52 controls). As there was no significant difference in the mean values of both the parameters between the right and left eyes, hence, for comparisons in the two groups and among different categories within the group, mean values of both eyes were obtained in both control and diabetics.

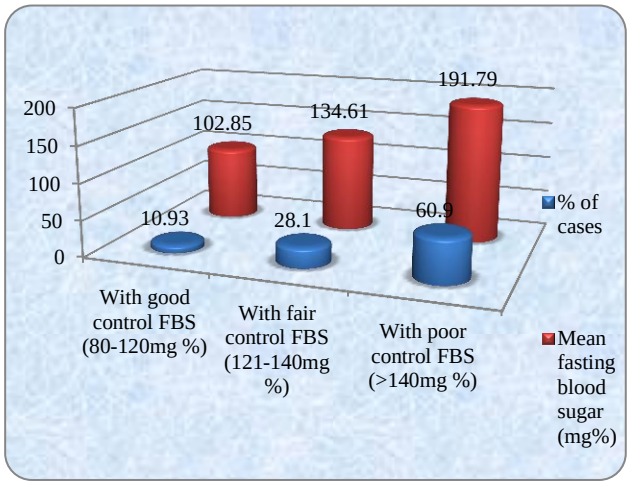
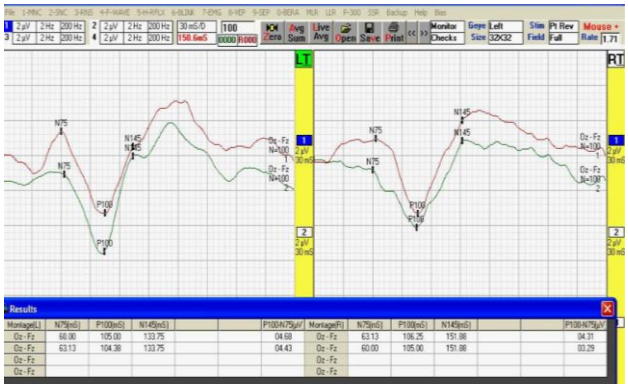


Figure 3: Distribution of patients and their mean fasting blood glucose levels in three categories of glycaemic control.



Monocular stimulation; check size: 54.6 minutes, reversal rate 1.71 Hz; band-pass 2-200 Hz; 100 epochs/sweeps averaged.

Figure 4: PRVEP record of a diabetic patient showing bilaterally prolonged P100 latencies.

Mean P100 latency and interocular latency differences revealed no statistically significant difference among different age-groups of diabetics, while reduction in mean N75-P100 amplitudes was statistically significant. With Tukey multiple comparisons, the difference was significant between the age-group of 21-40 years and >60 years, with p-value of 0.026 ($p<0.05$). Gender influence was found as increased mean P100 latency in the males with no statistical significance while increased mean N75-P100 amplitude was found in females with a statistical significance (p value of 0.01) as shown in Table 1.

Table 1: Mean P100 latency, mean N75-P100 amplitude and mean interocular latency difference in different age-groups and gender among the diabetics.

	Age-group			Gender	
	21-40 years	41-60 years	>60 years	Male	Female
Mean P100 latency(ms±SD)	103.28±1.18	105.76 ±7.23	104.92±7.65	105.43±7.09	104.60±7.81
Mean N75-P100 amplitude (µv± SD)	6.80±2.67	5.04±2.00	4.13±1.15	4.67±1.83	6.46±1.89
Mean interocular latency difference (ms±SD)	1.27±1.79	2.68±3.88	2.12±4.07	2.4 ±3.85	2.44±3.81

Mean P100 latency and mean interocular latency differences among various age groups of the cases were not statistically significant (one way ANOVA) with p value=0.860 and 0.721 respectively ($p>0.05$), while mean N75-P00 amplitude variations among the various age-groups were statistically significant ($p<0.05$). When compared in males in females, the increase in mean P100 latency in males was not found to be statistically significant p=0.77, whereas, increased mean N75-P100 amplitude among the females was statistically significant (zvalue=2.42),pvalue=0.01(<0.05).

Duration of the diabetes was found to influence the VEP parameters as statistically significant increase in the mean P100 latency with the duration of the disease (one way ANOVA). Tukey multiple comparison test revealed significant difference between the group 1 (<5 yrs) and group 3 (>10 years) with p value of 0.042. Mean N75-P100 amplitude was also found to be reduced with the duration of diabetes but the decrease was not statistically significant, p=0.656 ($p>0.05$) as in Table2.

Glycaemic status of the patients varied the mean P100 latency too, when compared among the three categories, but no statistical significance could be found for the increased values. Also, the variations in the mean N75-P100 amplitudes did not reveal statistical significance (Table 3).

Mean P100 latency found in the present study among the diabetics was 105.34±7.11 SD. Mean N75-P100 amplitudes was 4.86±1.9 SD, while mean inter-ocular latency difference was 2.42±3.8 SD. The differences in all the three VEP parameters tested and compared with the control group were found to be highly significant (Table 4).

Table 2: Mean P100 latency, mean N75-P100 amplitude in three categories with different duration of diabetes.

Duration of diabetes	No. of cases	% of cases	Mean P100 latency (ms±SD)	Mean N75-P100 amplitude (µv±SD)
<5 years	37	57.81	103.39±3.73	5.05±1.93
6-10 years	14	21.87	107.24±5.50	4.54±1.76
>10 years	13	20.31	108.85±12.71	4.68±2.05

Mean P100 latency increased with the duration of diabetes with statistically significant difference, p=0.029 (p<0.05). With Tukey multiple comparison test, significant differences were found between the group 1 (<5 years) and group 3 (>10 years) with p value=0.042. Mean N75-P100 amplitude reduced with the duration of diabetes but the decrease was not statistically significant, p=0.656 (p>0.05).

Table 3: Mean P100 latency and mean N75-P100 amplitude in three different categories of glycaemic control in diabetics.

Glycaemic control	No. of cases	% of cases	Mean P100 latency (ms±SD)	Mean N75-P100 amplitude (µv±SD)
Good control (80-120 mg %)	7	11.13	103.25±3.34	4.49±1.83
Fair control (121-140 mg %)	18	28	104.13±3.50	4.73±2.23
Poor control (>140 mg %)	39	60.9	106.28±8.61	5.0±1.79

Mean P100 latencies and mean N75-P100 amplitude differences in the three groups of glycaemic control were not found to be statistically significant (one way ANOVA) with p=0.240 (p >0.05) and p=0.763 (p>0.05) respectively.

Table 4: Comparison of mean P100 latencies, mean N75-P100 amplitude and mean interocular latency differences in controls and diabetics.

	Mean P100 latency (ms±SD)			Mean N75-P100 amplitude (µv±SD)			Mean interocular latency difference (ms±SD)
Subjects	No. of cases	Right eye	Left eye	Both eyes	Right eye	Left eye	Both eyes	
Diabetic	64	105.61±7.34	105.07±7.43	105.34±7.11	4.66±1.94	5.07± 2.12	4.86±1.90	2.42±3.8
Controls	52	98.23± 0.92	98.19± 1.19	98.21±0.96	6.84± 2.11	6.69± 2.03	6.76±1.99	0.64±0.71
Z-value	7.93				5.20			3.64
P value	0.000 (P<0.05)				0.000 (P<0.05)			0.001(P<0.05)

Mean P100 latency, N75-P100 amplitude and interocular latency differences among controls and diabetics were highly significant by z test (p value=0.000 for increase in the P100 latency and reduction in the amplitudes in the diabetics, while p=0.001 for interocular latency differences).

DISCUSSION

Peripheral neuropathy in diabetes and its correlation with the duration of diabetes and glycaemic control has been studied extensively. The evidence of visual pathway abnormalities in the diabetes as a part of the central nervous system involvement can expand the knowledge of electrophysiological influence of diabetes on the nervous system. Before the onset of microvascular lesions in diabetic retinopathy, the neural retina of diabetic eyes undergoes subtle functional changes not found to be detectable by fundus photography.[12] Analysis of pattern VEP responses may provide early diagnosis of such diabetic changes providing the subclinical evidence of visual dysfunctions which might help in avoiding the development of diabetic retinopathy by strict glycaemic control. Also, prognosis of the condition can be determined during the treatment.[13]

In the present study, the mean P100 latency in the diabetics was found to be significantly prolonged (105.34±7.11SD) when compared with those in the controls (98.21±0.96 SD) (Table 4). The above findings are in accordance with similar studies in the past including either Type 1 or Type 2 DM or both, without retinopathy. Yaltkaya K et al in 1988 investigated the possible effects of the disease on the central nervous system by PSVEP (pattern shift visual evoked potentials) in 25 diabetics excluding those with retinopathy, glaucoma and cataract. The latencies of P100 and N140 were observed to be prolonged.[14] Moreo G et al studied

18 NIDDM (non-insulin dependent diabetes mellitus) patients and compared with 35 normal subjects for VEP at the baseline and after 4.6±0.8 years to assess the possible progression over time. The peak P100 latencies were significantly delayed at the first recording with no significant alterations at the subsequent recording.[15] Dolu H et al in 2003, observed significant prolongation of P100 latency in 51 Type 2 diabetics as compared with 30 control subjects. [16]

A statistically significant reduction in the mean N75-P100 amplitude was also observed in diabetics in the present study as compared with the controls. Mean N75-P100 amplitude was 4.86µv±1.90 SD in the cases and that in controls it was 6.76 µv±1.99 SD with p value <0.001 (Table 4). Reduction in the mean N75-P100 amplitude values also conforms to other similar studies.[17-19] However, many studies also report no significant difference in the amplitude variations among the cases and controls.[20-25] The present study also demonstrated significantly increased mean interocular latency difference among the diabetics as compared to those in controls (Table 4). The mean value was 2.42 ms±3.83 S.D for the study group while for the control group it was found to be 0.64 ms±0.71 S.D. This conforms to the study by Moreo G et al in which the mean interocular latency difference in the diabetics was 4.6 ms±4.7 SD and in the controls it was 2.3 ms±1.7 SD (p value <0.02).[15] Thus, the present study demonstrates abnormalities in all the three PRVEP parameters tested, providing a significant prolongation of the mean P100 latency and interocular latency difference and also a significant reduction of mean N75-P100 amplitude in the diabetic patients even before the development of diabetic retinopathy.

The studies in the past have attempted to investigate the underlying cause for the VEP abnormalities in newly diagnosed as well as long-standing diabetes. Majority conclude that with different disease duration, retinal, macular and visual pathways functions are differently impaired in the diabetics without retinopathy. An early involvement of the innermost retinal layers has been suggested.[26] Also, a delayed neural conduction in the post-retinal visual pathways has been found. The two sources might contribute independently to the abnormal VEP responses in the diabetics whereas another similar study shows that the increase in the P100 latency exhibited by diabetic patients with little or no retinopathy usually reflect altered retinal function rather than optic neuropathy.[27,28] This can be considered as a sign of preclinical diabetic retinopathy, as no signs of diabetic retinopathy were detected on ophthalmoscopic examination. Early interventions in such patients can be started in the form of strict glycaemic control for a better prognosis.

With more prolonged hyperglycaemia, evidences of structural damage at the level of myelinated optic nerve fibers have been provided by the studies in the murine and human diabetic neuropathy.[29-31] Kamijo M et al in 1993 documented highly significant correlation of the prolongation of the VEP latencies with the structural lesions, namely, axonal atrophy and axoglial dysjunctions in the optic nerve.[31] A polyol pathway related mechanism has been implicated according to which, increased extracellular glucose concentrations produce a concentration dependent conversion of glucose to sorbitol by the enzyme aldose-reductase. Also, there occurs an associated depletion of myo-inositol in nerve, which may also be due to sodium and sodium-related metabolic alterations in the nerve causing competitive inhibition of sodium gradient dependent MI (myo-inositol) uptake. Nerve MI depletion, in turn reduces the activity of Na^+K^+ATP-ase (sodium potassium ATP-ase) which is thought to be located primarily in the nodal and paranodal regions of large myelinated nerve fibers. Reduced Na^+K^+ATP-ase activity leads to increase in the axonal Na^+ concentration, reduced nodal Na^+ permeability and selective conduction block with diminished conduction velocity. These metabolic sequelae have also been suggested to be present in diabetic optic nerve.[31] They also examined the treatment effects of the aldose reductase inhibitor, Ponalrestat. The regimen resulted in complete prevention of axoglial dysjunctions but had no effect on axonal atrophy.

Thus, the prolongation of P100 latencies observed in diabetics in the present study could be a manifestation of structural damage at the level of the myelinated optic nerve fibers or retinal ganglion cell damage before the development of diabetic retinopathy. A significant correlation of VEP abnormalities with the duration of the disease was found, which is in line with majority of the researchers.[14,16,32-34] No correlation could be found out with the glycaemic status of the diabetics and the VEP abnormalities, the relationship which although studied by many authors, yet could not be stated as significant by the majority.[15,35-40]

CONCLUSION

Visual evoked potentials are deranged in diabetic patients without any clinical evidence of retinopathy or other ocular diseases, thus detecting preclinical changes within or upstream the retina in the diabetics. PRVEPs, by a sensitive detection of early visual dysfunctions enable expanding our knowledge of electrophysiological and neural functions within the wider field of the effect of diabetes on the central nervous system. PRVEPs should be recommended in the diabetics for a complete assessment and a better prognosis of the condition. However, more researches evaluating the role of the glycaemic status of the diabetics and its relationship with the VEP abnormalities are necessitated.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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