# Visual evoked potential as an early marker of diabetic retinopathy

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## Abstract

**Background**: Chronic hyperglycemia in diabetes mellitus causes damage to various organs, particularly eyes, kidneys, nerves, heart, and the blood vessels. Visual defects in diabetics occurs due to both vascular and metabolic abnormalities which can affect retina, optic nerve and visual pathway. Change in Visual evoked potential (VEP) response occurs in diabetic patients much earlier than development of overt retinopathy and these changes correlate with duration of disease. Aim of this study was to determine the subtle functional changes in the retina of diabetic eye with the help of VEP before diabetic retinopathy sets in. In the current study comparison between amplitudes, latency P100 of VEP in type 2 diabetes mellitus with that of healthy controls was done.

**Method**: Cross sectional study using 100 controls and 100 diabetic patients was carried out in the department of Physiology Deccan college of Medical Sciences, Hyderabad. Statistical analysis was done using SPSS software.

**Result:** Significant association was obtained between duration of diabetes mellitus and P100 latency.

**Conclusion**: VEP can be used as a very useful electrophysiological indicator of early subtle functional changes of retina in diabetes mellitus.

**Keywords**: Diabetes mellitus, Visual evoked potential, P100 latency, P100 amplitude

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## Introduction

Type -2 diabetes mellitus (DM) is one of the most serious challenges to healthcare.[1] Chronic hyperglycemia of diabetes is connected with continuing damage, dysfunction or malfunction of various organs, particularly eyes, kidneys, nerves, heart and the blood vessels. It is well known that patient's will develop peripheral and autonomic neuropathy.[2] Peripheral nervous system involvement in diabetes is well known, but there are not many studies on Central nervous system involvement. Recent reviews have suggested that diabetics may also suffer from central neuropathy or the degeneration of the central nervous system. Visual defects in diabetes occur due to both vascular and metabolic abnormalities which can affect the retina, optic nerve, and the visual pathway.[3]

Visual dysfunction in DM is multi factorial and depends on predominant pathophysiological factors in various stages of the diseases.[5] One of the primary goals of management in diabetic patients is to avoid the risk of diabetic retinopathy, by maintaining blood glucose levels nearly in the normal range.[6] Before the onset of micro vascular lesions, the retina of the eye undergoes subtle functional changes that are not detec Table by fundus photography.[7]

Evoked potentials constitute a relatively new method of clinical neurophysiology, allowing functional evaluation of the nervous system. The non-invasive methods give information about the functional state of different tracts with in the central nervous system, particularly when the clinical signs and the results of neuroimaging methods are either non informative or non-conclusive.[8] Visual evoked potentials (VEP) is a sensitive, noninvasive test to spot central demyelination of optic nerve.[11]

Analysis of pattern VEP responses may provide early diagnosis of such diabetic changes and determine prognosis during treatment. Pattern VEP (PVEP) can detect any defect from the optic nerve to the occipital cortex.[7]

Recording VEP from scalp is a highly sensitive, reliable, and reproducible method for diagnosing conduction defects in the anterior visual pathways. The visual neurons respond selectively to visual patterns of progressively greater complexities.[4,9] Various clinical conditions in which delayed VEP latencies are of diagnostic importance include multiple sclerosis, retro bulbar neuritis, papillitis, hereditary toxic and nutritional optic neuropathies. Spuriously prolonged VEP latencies are observed with ocular causes glaucoma or conditions affecting conducting media of eyes like cataract, vitreous opacities and retinal diseases.[4] Amplitude values decrease progressively and latency values increase progressively in diabetes as the years pass. Progressive delay in VEP latency values

specify retinal ganglion cell damage, which happen even before the first opthalmoscopically noticeable signs of diabetic retinopathy arise. The prolongation of P100 latencies, which are observed in diabetics, is thus an indication of structural damage at the level of the myelinated optic nerve fibers.[9] VEP should be recommended whenever feasible and must be added along with the list of screening tools for a more complete and early assessment of the neurological involvement in diabetics patients, to counsel them for an early and proper management of disease.

## Materials and Methods

To conduct this cross sectional comparative study, a population of 100 healthy individuals and 100 patients with known history of type 2 diabetes mellitus either on treatment or discontinued treatment had been selected from Medicine department of Princess Esra Hospital located in the city of Hyderabad, India. Prior to recruitment informed consent was obtained from all the subjects and the study was approved by the ethics committee of Deccan College of Medical Sciences.

**Inclusion criteria:**

1. Normal healthy individuals willing to join the study.
2. Patients with known history of type 2 diabetes mellitus either on treatment or discontinued treatment.

**Exclusion criteria:**

1. Subjects having a history of neurological disorder.
2. Subjects having glaucoma, cataract, any evidence of optic atrophy and a visual acuity of less than 6/18 even with corrective lenses are excluded from study.

**Data Collection**

The study was conducted after getting clearance from the ethical committee. A detailed history taking and thorough ophthalmoscope examination of patients were done after which they were subjected for VEP assessment.

## Results

The data obtained was tabulated and analyzed by using SPSS software.

**Tables 1: Distribution of Diabetes according to age (N=100)**

| Age in years | Number | Percentage |
|---|---|---|
| <40 | 2 | 2 |
| 41-50 | 23 | 23 |
| 51-60 | 50 | 50 |
| 61-70 | 25 | 25 |
| Total | 100 | 100 |

In the present study 50% of the diabetes were in the age group of 51-60 years and 25% 0f them belonged to 61-70 years. The rest 25% of them belonged to 61-70 years. The rest 25% of them belonged to < 50 years. The mean age of cases was calculated as 55.8+/-7.001.

**Table 2: Distribution of Diabetes according to gender (N=100)**

| Gender | Frequency | Percentage |
|---|---|---|
| Male | 53 | 53 |
| Female | 47 | 47 |
| Total | 100 | 100 |

Out of the 100 diabetic cases 53 were males and 47 were females.

**Table 3: Distribution of control according to age (N=100)**

| Age (in years) | Number | Percentage |
|---|---|---|
| <40 | 3 | 3 |
| 41-50 | 27 | 27 |
| 51-60 | 54 | 54 |
| 61-70 | 16 | 16 |
| Total | 100 | 100 |

In the present study 54% of the diabetes were in the age group of 51-60 years and 16% of them belonged to 61-70 years. The rest 27% of them belonged to < 50 years. The mean age of controls calculated was 55.13+/- 6.35.

**Table 4: Distribution of diabetic cases according to latency of P100 (N=100)**

| P100(in m sec) | Number | Percentage |
|---|---|---|
| <100 | 0 | 0 |
| 100-120 | 21 | 21 |
| >120 | 79 | 79 |
| Total | 100 | 100 |

Mean value of P100=127+/-3.147

Out of the 100 diabetic cases, 79 had P100 latency more than 120ms and 21 had normal P100 value i.e. between 100-120 ms. None had P100 latency value less than 100ms. The mean value of P100 among diabetic cases was found to be 127.67ms with standard deviation of 3.147.

**Table 5: Distribution of controls according to latency of P100**

| P100(in m sec) | Number | Percentage |
|---|---|---|
| <100 | 18 | 18 |
| 100-120 | 70 | 70 |
| >120 | 12 | 12 |
| Total | 100 | 100 |

Mean value of P100=107.36+/-2.84

Out of the 100 controls, 70 had normal P100 latency between 100-120 ms and 12 had P100 value more than 120 ms. Eighteen of the controls had P100 latency value less than 100ms. The mean value of P100 among controls was found to be 107.36ms with standard deviation of 2.84.

**Table 6: Mean and standard deviation of amplitude of P100 among cases and controls**

| P100 | Cases | Controls |
|---|---|---|
| Mean | 6.145 | 6.637 |
| Standard Deviation | 0.79 | 0.81 |

The mean amplitude of P100 among cases was 6.145 with a standard deviation of 0.79 and among control were 6.637 with a standard deviation of 0.81.

Bivariate analysis among cases and controls with respect to age, sex, and p100 latency

**Table 7: Comparison of diabetic cases and controls with respect to age**

| Age(years) | Diabetics | Controls | Total |
|---|---|---|---|
| >40 | 2 | 3 | 5 |
| 41-50 | 23 | 27 | 50 |
| 51-60 | 50 | 54 | 104 |
| 61-70 | 25 | 16 | 41 |
| Total | 100 | 100 | 200 |
| $X^2$=2.6495p>0.448 | | | |

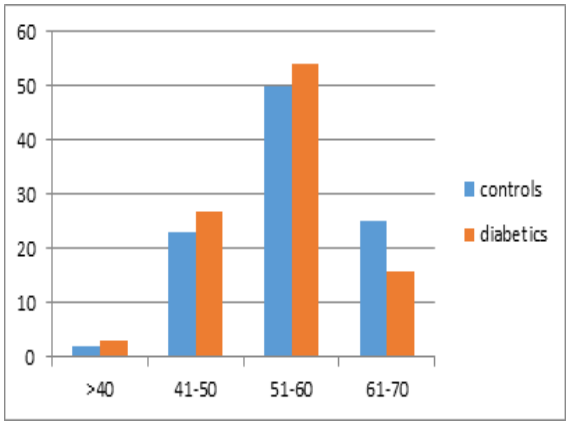


**Fig. 1**

In the present study, numbers of subjects in the diabetic as well as control group were comparable and hence difference among them was statistically not significant.

**Table 8: Comparison of diabetic cases and controls according to gender**

| Gender | Diabetes | Control | Total |
|---|---|---|---|
| Male | 53 | 52 | 105 |
| Female | 47 | 48 | 95 |
| Total | 100 | 100 | 200 |
| $X^2$=1.02p=0.85 | | | |

Similar to age, the diabetes and control group were comparable with respect to gender.

**Table 9: Comparison of diabetic cases and controls according to P 100 latency (ms)**

| P 100 latency | Diabetics | Control | Total |
|---|---|---|---|
| >120 | 71 | 12 | 159 |
| <120 | 29 | 88 | 41 |
| Total | 100 | 100 | 200 |
| $X^2$=71.69 p<0.05 | | | |

Out of the 100 diabetic cases, 71 had P100 latency more than 120 millisecond and 29 had a latency <120ms. Among the controls, 12 had a P100 latency >120ms and 88 had normal P100 latencies. There was very significant difference between P100 latencies of case and P100 latency was increased among diabetes.

Out of the 100 diabetic cases, 72 had P100 amplitude>/-6µv and 28 had amplitude <6µv. Among the controls, 81 had P100 amplitude >/- 6µv and 19 had an amplitude <6 µv. there was no significant difference between P100 amplitudes of cases and controls.

Association between duration of diabetes and p100

**Table 10: Association of P100 Latency with duration of Diabetes**

| Duration of diabetes in years | P100 Latency 100-120ms | >120ms | Total |
|---|---|---|---|
| 1-5 | 19 | 28 | 47 |
| 6-10 | 2 | 23 | 25 |
| 11-15 | 0 | 20 | 20 |
| 16-20 | 0 | 8 | 8 |
| Total | 21 | 79 | 100 |
| Fischer exact=20.68 P<0.00 1 | | | |

A very significant correlation was obtained between duration of diabetes mellitus and latency of P100.

In the present study 50% of the diabetics were in the age group of 51-60 years. The mean value of latency of P100 among diabetic was found to be 127.67 +/- 3.147. The mean value of latency of P100 among controls was found to be 107.36+/- 2.84. There was a significant difference between the P100 latencies of cases and controls and P100 latency was increased among diabetics (p<0.05). The mean value of amplitude of P100 among cases was 6.145+/- 0.79 and that of controls was 6.637+/-0.81. Bivariate analysis showed that there was no significant difference in the amplitudes of P100 among cases and control. A very significant association was obtained between duration of diabetes mellitus and P100 latency. But no association was obtained between P100 amplitude and duration of diabetes mellitus.

## Discussion

Visual insufficiency in general is a result of both vascular and metabolic abnormalities in Diabetes mellitus, which can harmfully affect the retina and visual pathways. The visual evoked potential (VEP) is a non-invasive neuro physiological examination for evaluating the integrity of neural pathways, responsible for vision.[12] Early detection of diabetic retinopathy changes by VEP can prevent the loss of vision.

The visual evoked responses can be quantified by measuring peak amplitudes and latencies and they provide numerical data that are quantitative extensions of neurological examinations.[12] There is great inter-individual variations in the amplitudes of VEPs compared with latency of responses. The VEP amplitude can be modified by attention, cranial shape, distribution of sulci of brain and size of the brain.[13] In diabetics the latency values have a tendency to prolong with time, which could be due to damage to ganglion cells.[14]

The P100 is a prominent peak that shows relatively less variation between the subjects, minimal with inter ocular difference and negligible variation with repetitive measurements over time. The wave N75 is a sign of the activity of fovea and the primary visual cortex while N135 reflects the activity of visual association area.[15]

The objectives of this cross sectional comparative study were to compare VEP in 100 Diabetic patients with that of 100 normal controls and to find out any possible correlation with type 2 Diabetes Mellitus and VEP. The study was conducted in the department of Physiology Deccan College of medical Sciences. Data was analyzed using SPSS software.

In the present study age of cases was 55.81 +/- 7.001 and that of controls was 55.13+/- 6.35(Table 1,3). Out of the total subjects there were 53 males 47 females among cases and 52 males and 48 females among controls.[Tables 2,4]

The mean value of amplitude of P100 among cases was 6.145+/-0.79 and that of controls was 6.637+/- 0.81. Bivariate analysis showed that there was no significant difference in the amplitudes of P100 among cases and controls [Tables 4].

In our study, out of the 100 diabetic cases, 79 had P100 latency more than 120 ms and 21 had normal P100 value (i.e. between 100-120ms.). None had P100 latency value less than 100ms. The mean value of P100 among diabetic cases was found to be 127.67 with standard deviation of 3.147 [Table 4].

Out of the 100 controls, 70 had P100 latency between 100-120ms and 12 had P100 value more than 120ms. Eighteen of the controls had P100 latency value less than 100ms. The mean value of P100 among controls was found to be 107.36 with standard deviation of 2.84 [Table 5].

In the present study bivariate analysis showed that the P100 latency was prolonged among case than controls and there was a significant positive correlation, between P100 latency and diabetes mellitus ($p<0.05$) [Table 9]. Also a significant association was observed between duration of diabetes mellitus and P100 latency, but not with amplitude of P100 [Table 10].

Two factors may contribute to the delay in P100 latency: the first related to the innermost retinal layers and the second related to an impairment of the neural conduction at post retinal level. Both these factors may contribute in parallel to increased P100 latency.[16]

In diabetes mellitus, damage occurs to ganglion cell layer which can be due to extracellular glutamate accumulation, leading to functional and anatomical changes, which rise even before the vascular damage. Oxidative stress, besides micro vascular abnormalities and consequences of glucose metabolism, play a great role in the pathological progress of diabetic retinopathy. That might be due to either an increase in free radical and oxidant production or reduced activity of anti-oxidative mechanisms, considered as a sign of preclinical diabetic retinopathy.[10]

## Conclusion

The visual evoked potential is a very useful electrophysiological indicator of premature visual changes in diabetes and it helps to assess the integrity of the visual pathway. The VEP are electrical potential differences recorded from scalp, in response to visual stimuli, and are used to review the visual pathway, which extend from retinal ganglion cells to the visual cortex.

VEP measurement shows the involvement of anterior visual pathway, before the development of retinopathy. Contrary to the other ophthalmological studies, VEP is a very sensitive method to monitor the first phase of diabetes, particularly to determine its bad effects on visual function. Moreover this tool is recommended as an early chance for the proper management of this metabolic illness, which can bring about blindness. Our study compared VEP among 100 diabetics and equal number of healthy controls. We observed that P100 latency was prolonged significantly in diabetic patients when compared with healthy controls.

Since prolongation of P100 latency in diabetes is a remarkable sign for the development of optic neuropathy, we recommend a routine yearly VEP assessment to all the diabetic patients, for the early identification of visual defects, for a more complete and early assessment of the neurological involvement in diabetic patients, to counsel them for an early and proper management of the disease.

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