

# Study of Cognitive Evoked Potentials in Type 2 Diabetes Mellitus

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## Abstract

**Background:** The complete syndrome of diabetes mellitus, related metabolic aberrations and diabetic complications is posing a major threat in the 21<sup>st</sup> century. Cognitive dysfunction is a well known complication of diabetes which continues to be investigated.

**Aims and Objectives:** To evaluate the cognitive functions using electrophysiological (P<sub>300</sub> latencies) tests in diabetics and non diabetics in the age group of 40 - 59 years with same gender proportion, to analyze whether cognition is affected in diabetics when compared to non diabetics and to know the usefulness of electrophysiological (P<sub>300</sub> latencies) tests in detecting subtle cognitive changes.

**Materials and Method:** The study was conducted on 50 diabetics and 50 non diabetics aged between 40 and 59 years. Cognition was assessed using P<sub>300</sub> potential. The evoked potential data analysis was done using Student unpaired T test to compare the mean of two groups.

**Results:** The absolute peak latencies of P<sub>3</sub> component of endogenous cognitive evoked potentials was significantly prolonged among diabetics ( $334.8 \pm 20.8$ ) as compared to controls ( $285.7 \pm 14.9$ ). There was no statistically significant difference between groups when analyzed for N<sub>2</sub> in C<sub>z</sub> and F<sub>z</sub>.

**Conclusion:** This study identifies prevalence of cognitive dysfunction in diabetic patients when assessed using electrophysiological tests. Good cognitive function is critical to safely manage diabetes and draws attention to various challenges in their management. Clinicians should consider screening for cognitive function in diabetics using P<sub>300</sub>, as it is effective in detecting subtle changes much before their clinical manifestation.

**Key words:** Diabetes Mellitus; Cognition; Cognitive evoked potential; Event related potentials; NIDDM; P<sub>300</sub>

## Introduction

Diabetes mellitus (DM) is taking its place as a main threat to human health in the 21<sup>st</sup> century. Type 2 DM is a complex metabolic disorder that results from

an interaction between genetic predisposition and environmental factors. It accounts for about 90% of all cases of diabetes.<sup>1</sup> The prevalence of DM is rapidly increasing as a result of longevity, urbanization, traditional family structure, mechanized work and associated lifestyle changes.<sup>2</sup>

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The number of people with DM worldwide has increased more than two fold over the past three decades. In 2011, approximately 366 million people worldwide had DM, 90% of whom had type 2 DM. The number of people globally with DM is estimated to be 552 million (87 million in India) by 2030, which will represent

7.8% of the total adult population of the world in the age group of 20–79 years. The major burden of DM is in developing countries. 80% cases of DM live in less developed countries.<sup>3</sup> DM is known to have devastating complications on multiple organs in the body. The chronic course of DM is associated with renal, retinal, cardiovascular, nervous system complications like brain hemorrhage, ischemia, peripheral and autonomic neuropathy.<sup>4</sup> Higher brain activities like message comprehension and mnemonic capacities have not been monitored in diabetics due to non availability of biological markers.<sup>5</sup>

A well recognized nervous system complication of elderly diabetics which is less addressed is cognitive dysfunction.<sup>6</sup>

Cognitive impairment in diabetes in terms of speed of processing, memory and attention was observed in patients with DM especially during hyperglycemia.<sup>7</sup>

Cognitive P<sub>300</sub> potential has been used as a non-invasive, objective and quantitative method to assess higher cognitive functions of human brain. These potentials express the aptitude of human brain to discriminate, classify, decide and memorize the significance of an exogenous stimulus. It serves as a tool to check the sequelae caused by hypoglycemia in hippocampus region, which is evident even before there is clinical manifestation of nervous system damage.<sup>8,9</sup>

Concomitant cognitive dysfunction in diabetic patients generally goes unnoticed. Cognitive dysfunction is an important co morbidity that needs to be addressed in diabetic population. This aroused the need for screening subtle cognitive dysfunction in diabetics which are often unrecognizable.

Recognizing these asymptomatic cerebral changes and modifiable risk factors that influence cognitive changes in diabetes can put forward preventive treatment of the condition and thereby improve the quality of life so as to - “Achieve tightest possible glycemic control with lowest possible chances of hypoglycemia”.

## Materials and Method

The present study was conducted in the auspices of research laboratory of Department of Physiology, S.S. Institute of Medical Sciences & Research Centre, Davangere. Study design was of case control type.

### Selection of participants:

- The study comprised of 100 randomly selected subjects in the age group of 40 – 59 years.
- The case group comprised of 28 diabetic males and 22 diabetic females.
- The control group included 30 non diabetic males and 20 non diabetics females in the same age group.

### Inclusion criteria:

#### ❖ Cases:

- Known diabetic between 40 and 59 years of age.
- Newly diagnosed cases between 40 and 59 years of age.

#### ❖ Controls:

- Non diabetics between 40 and 59 years of age in same gender proportion.
- Same socioeconomic and educational background as diabetics.

### Exclusion criteria

- Hearing loss.
- Old age (above 60 years)-Dementia, Alzheimer’s disease.
- Stroke.
- Recurrent hypoglycemic episodes.
- Parkinson’s disease.
- HIV dementia complex.
- Psychiatric disorders like Schizophrenia and depression.
- Nutritional deficiency - Vitamin B<sub>12</sub>.
- Hepatic encephalopathy.
- Alcoholism.

After obtaining Institutional ethics committee approval and written informed consent, the patient’s blood glucose levels were estimated to check their glycemic status on the day of cognitive assessment

Electrophysiological test was recorded using RMS EMG EP MARK II supplied by recorders and medicare system (P) limited, Chandigarh.

**Data Analysis**

Data analysis was done using SPSS software. Student unpaired T test to compare the mean of evoked potentials between the two groups. Differences were considered significant at  $P < 0.001$ .

**Results**

The study was conducted among diabetics and non diabetics to find out relationship between diabetes and cognition, in the age group of 40-59 years. The data was analyzed by using SPSS 18 and excel was used to generate graphs, tables etc.

Analysis was done using appropriate statistical tests to compare mean values of different parameters between 2 groups. P value was significant at  $\leq 0.001$ . Mean and standard deviation were calculated for baseline characteristics and electrophysiological test. Cases and controls were compared using Student's unpaired T test. Table 1 shows the comparison between the baseline characteristics of subjects. Table 2 shows the Comparison of cognitive evoked potential in study group and control group. It shows that the absolute peak latencies of  $P_{300}$  component of endogenous cognitive evoked potentials was significantly prolonged among diabetics as compared to controls. Graph 1 illustrates that Amplitude of  $P_{300} - N_2$  is higher in cases than that of controls.

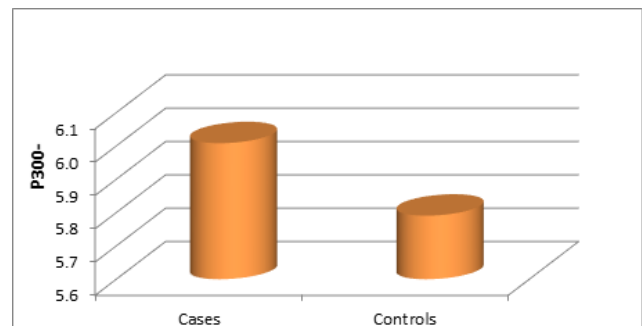
**Table 1: Baseline physical characteristics.**

Parameter	Case	Control	P* Value
Age (Years)	52.7+7.1	50.06+6.3	0.052
Pulse (bpm)	73.8+7.1	74.72+6.1	0.46
SBP (mmHg)	127.6+13.0	126+7.6	0.45
DBP (mmHg)	77.8+6.2	79.2+4.0	0.17
BMI (Kg/m2)	25.3+3.5	23.9+3.1	0.03
* Student's unpaired t test,			

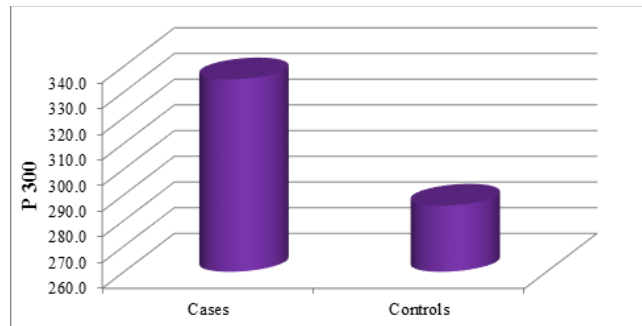
**I. Comparison of cognitive evoked potential in study group and control group.**

**Table 2. Cognitive evoked potential.**

Parameter	Cases	Controls	P* Value
N100 latency (ms)	76.0 + 20.9	77.4 + 19.5	0.73
P200 latency(ms)	167.3 + 26.3	165.4 + 29.3	0.73
N200 latency(ms)	185.0 + 31.2	179.7 + 29	0.30
P300 latency(ms)	334.8 + 20.8	285.7 + 14.9	<0.001*
P300-N2( $\mu$ V)	6.0 + 3.8	5.8 + 4.7	0.79
* Student's unpaired t test, P < 0.001			



**Graph 1: Amplitude of  $P_{300} - N_2$  among cases and controls.**



**Graph 2: Latency of  $P_{300}$  among cases and controls.**

Mean  $P_{300}$  latency for case group was 334.8+20.8ms and that of controls was 285.7+14.9ms. The difference was highly significant with a P value of <0.001. There was no significant difference in amplitude of  $P_{300} - N_2$ , latencies of  $N_2$  and  $P_2$ .

**Discussion**

The diabetic patients complain of loss of memory and poor ability to concentrate. Self management of diabetes including avoidance of hypoglycemia is complex. The cerebral mechanism underlying the cognitive deficits and the responsible brain structures remains to be delineated. They are the topics of intense research, but brain atrophy and vascular changes have

both been assumed.<sup>10</sup>

In previous studies,  $P_{300}$  latencies in diabetics were either prolonged or tend to be prolonged in  $C_z$  and  $F_z$  compared to controls.<sup>11,12</sup> In a study  $P_{300}$  latency was not elevated significantly at all sites but longer latency was observed at  $F_z$  and  $C_z$ .<sup>13</sup>

Concerning the amplitude of  $P_{300}$  the data are sparse. Most authors did not report measurement of amplitude<sup>14</sup>.<sup>12</sup> In others, there was no statistically significant difference between patients and control.<sup>15</sup>

In our study absolute peak latencies of  $P_{300}$  component of endogenous cognitive evoked potentials was significantly prolonged among diabetics as compared to controls. The amplitude did not differ significantly in the two groups.

The  $N_{100}$  and  $P_{200}$  components are believed to reflect the activity in neural areas that are activated by sensory modality and are independent of the attention of the subject.<sup>16</sup> The  $N_{200}$  component is related to the unexpectedness of the stimulus. It is regarded as a measure of the time of early stimulus processing, engaging orientation and attention.  $P_{300}$  latency is regarded as a measure of stimulus classification, speed, reflection of memory and storage that are initiated in the hippocampus which is considered to be  $P_{300}$  generator. The  $P_{300}$  amplitude represents online updating of working memory and / or attention process involved in working memory.<sup>17,18</sup>

Since the latencies of  $N_{100}$ ,  $N_{200}$  and  $P_{200}$  did not differ between cases and controls, prolongation of  $P_{300}$  latencies cannot be attributed to delay in perceptual encoding. It is thought to be produced by interaction between frontal lobe, hippocampus, temporal and parietal process. Hippocampus is involved in learning and memory. The delayed  $P_3$  in NIDDM therefore reflects inhibition or possible damage of this area.<sup>14</sup> Diabetic milieu causes delay in cognitive processes by interacting with  $N_{200}$  and  $P_3$  generators in cerebral cortex.<sup>17</sup>

The observed electrophysiological abnormality reflects impairment in attention, memory and speed of information processing which is indicative of early cognitive impairment in diabetes.

Medical care alone in the absence of adequate self-care is rarely effective for chronic illnesses like Diabetes. Self care in diabetes has important clinical

and public health implications<sup>19</sup> Since the incidence of Alzheimer's disease is increasing in diabetics, assessing cognitive function is very essential in preventing this co morbidity in the elderly diabetics.<sup>6</sup> Older women with diabetes have poorer cognitive functioning and a more rapid cognitive decline than women with normal blood glucose level.<sup>20</sup> Studies show that improving the metabolic control in IDDM patients with vigorous and continuous insulin, further deteriorates their cognition.<sup>21</sup>

### Limitations of the Study

- The present study is a case control study where subjects were randomly selected from population. A large population based study is required to extrapolate these findings to general population.
- The study does not correlate glycemic status and duration of diabetes mellitus with that of cognitive function, which would establish a better association of cognitive function and glycemic status.

### Conclusion

The aim of this study was to assess cognitive function in type 2 DM and to find out the usefulness of electrophysiological tests in detecting cognitive changes.

In general we found that there was statistically significant difference in  $P_{300}$  latency between diabetics and non diabetics, with higher latency in diabetic group when compared to non diabetic group. The amplitude did not differ among the two groups. These results prove that diabetes affects cognition. The cognitive impairment was evident with electrophysiological tests. This highlights the fact that electrophysiological tests are highly sensitive in detecting early cognitive impairment in diabetic patients.

**Conflicts of Interest:** None

**Source of Funding:** No Funding

**Ethical Clearance:** Institutional ethics committee clearance was obtained before the start of the study.

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