*International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)*
*An Online International Journal Available at http://www.cibtech.org/jms.htm*
*2013 Vol. 3 (1) January-April, pp.24-28/ Singh et al.*
***Research Article***

# STUDY OF EFFECT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTIONS BY EVENT RELATED POTENTIAL P300

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## ABSTRACT
The study was conducted to investigate the influence of type 2 diabetes mellitus on cognitive functions by measuring event related potential P300 (ERP P300) in 30 patients of type 2 diabetes mellitus aged 46-75 years with disease duration more than 5 years and compared them with control group. Diabetics had significantly longer P300 latency which was neither correlated with plasma glucose level nor with duration of disease. P300 amplitude was significantly reduced in diabetics. Thus ERP P300 can be very useful in detecting cognitive decline early in course of diabetes.

***Key Words****: Diabetes Mellitus Type 2, Cognition, ERP P300*

## INTRODUCTION
Type 2 diabetes is due to defect in insulin production and its action which can result in cognitive dysfunction (Alvarenga *et al.,* 2005). Cognition is the process of obtaining, organizing and using intellectual knowledge. It is a sequence of mental operations involving input and storage of information along with calling up and processing relevant information from stored memory (Kaplan & Sadock's Synopsis of psychiatry, behavioral sciences / clinical psychiatry, 2007). Few studies used conventional cognitive tests like Mini Mental State Examination, Digit Symbol Test and Trail B Test and demonstrated that diabetes is associated with lower levels of cognitive functions (Gregg *et al.,* 2000; Kalmijn *et al.,* 1995). But when a relatively new electrophysiological cognitive test Event Related Potential (ERP) P300 was used, conflicting results were obtained. Few studies observed that there was no significant association between type 2 diabetes and altered cognitive functions tested by P300 (Kurita *et al.,* 1995; Tandon *et al.,* 1999; Dey *et al.,* 1997) while Cosway et al (2001) found no significant change in P300 in type 2 diabetes. Therefore the present study was undertaken to investigate the influence of diabetes mellitus on cognitive functions assessed by ERP P300.
ERP is the external recording of the endogenous electrical activity of the underlying brain structure resulting from a stimulus bound activity. P300 is recorded by using oddball paradigm, in which subject is attentive and consciously distinguish an acoustic stimulus (target/rare) from a group of other acoustic (nontarget/frequent) stimuli (Alvarenga *et al.,* 2005). ERPs consist of a series of positive and negative waves that are generated above the brainstem. With frequent tone, a negative N1 – positive P2 complex is seen. With rare stimulus, a negative N1- positive apparent P2 – negative N2 – positive P3 complex is seen. The P3 (P300) component of this response has latency of nearly 300 – 350 ms following the onset of rare stimuli and is of positive polarity (Goodin *et al.,* 1994). P300 latency is an index of processing time required before response generation; so it is a sensitive temporal measure of neural activity underlying the process of attention allocation and immediate memory (cognitive functions). P300 latency is negatively correlated with mental function in normal subjects, with shorter latencies associated with

superior cognitive performance. P300 amplitude vary from 5-20 microvolt (µV) but may reach up to 40 µV. P300 amplitude is proportional to attention given to a task and high amplitude has been associated with superior memory performance. P300 amplitude can be viewed as measure of CNS activity that reflects the processing of incoming information when it is incorporated into memory representation of stimulus and the context in which the stimulus occurs (Polich, 1998).

## MATERIALS AND METHODS

Institutional ethical committee cleared the protocol. Subjects were divided into two groups. Group I (test group) was comprised of 30 patients (M:20, F:10) of type 2 diabetes in age group more than 40 years (range 46-75 years) with disease duration more than 5 years and on drug treatment attending Medicine OPD of a North Indian Medical College. Patients of hypertension, severe anemia, deafness, any psychiatric & neurological disorder or subjects taking any drug other than drugs for diabetes were excluded. Group II (control group) was comprised of age and sex matched 30 control subjects (healthy volunteers).

### *Procedure for P300*

Subjects were informed about nature of procedure and informed consent was taken. The subject was made to lie down comfortably and relaxed on a couch in a soundproof room with closed eyes. Rare tone (2 KHz) and frequent tone (1 KHz) of 85dB were applied on both ears together in 20% and 80 % in frequency in random through headphones. Total 300 stimuli were applied at rate of 1 stimuli/sec (Alvarenga *et al.,* 2005; Kurita *et al.,* 1995; Mavioglu *et al.,* 1999). Band pass filter was 0.2 -100 Hz (Goodin *et al.,* 1994). The volume conducted evoked responses (bioelectrical signals) were picked up from the scalp by using Ag/AgCl electrodes placed as per 10–20 International system of placement (Tandon *et al.,*1999; Cosway *et al.,* 2001 ). The recording sites on scalp were cleaned with alcohol or spirit. After applying electrolyte paste on recording surface of Ag/AgCl electrodes, one active electrode was attached on vertex (Cz), one as ground electrode to forehead (Fz) and two reference electrodes to right and left mastoid designated as A1 and A2 respectively. All the electrodes were plugged to a junction box keeping skin to electrode impedance below 5 K ohms. Subjects were asked to avoid sleep and identify the rare stimulus, counting in loud voice. Responses with artifacts were automatically rejected (Alvarenga *et al.,* 2005; Kurita *et al.,* 1995; DeGiorgio *et al.,* 1993). The signals were picked by electrodes and were filtered, amplified, averaged, displayed on the screen of EMG EP MK II equipment (Electromyography, Evoked potential machine, MK II model, Recorders and Medicare System Private Ltd. Chandigarh, India) and recorded. Two reproducible recordings were taken for a subject and averaged together to obtain the final measurement (Goodin *et al.,* 1994 and Polich, 1998). Latencies of P2, N2, P3 and amplitude of P300 waves were measured.

### *Glycemic Levels*

Fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) were measured in all subjects before the test.

### *Statistics*

All the data so obtained was analyzed statistically by using 'Student's t-test' and 'Pearson's correlation of coefficient' were calculated between various parameters by using SPSS version 10.

## RESULTS

Both groups (control and test) were age and sex matched. The differences in height, blood pressure and hemoglobin of test and control groups were not significant. Weight and body mass index; fasting blood sugar and postprandial blood sugar levels were significantly higher in test group (table 1). Test group had significantly higher P300 latency than control group ($p < 0.001$). There was significant increase in P300 latency in males & females of test group in comparison with males & females of control group (table 2). Test group had significantly decreased P300 amplitude than control group ($p < 0.001$) as well as there was significant decrease in P300 amplitude in males & females of test group in comparison with males &

females of control group (table 3). There was no significant correlation between P300 latency and age of control, FPG, PPPG and duration of diabetes (table 4).

**Table 1: Comparison of sociodermographic and biochemical parameters of control and test groups**

| Parameter | Control (n = 30) | Test (n = 30) | P values |
|---|---|---|---|
| Age (years) | 56.23 ± 5.59 | 57.86 ± 7.82 | > 0.05* |
| Weight (Kg) | 62.83 ± 6.87 | 68.66 ± 11.19 | < 0.05** |
| Body mass index | 23.77 ± 2.55 | 26.31 ± 4.16 | < 0.05** |
| FPG (mg %) | 84.76±7.43 | 139.6 ±37.86 | < 0.001** |
| PPPG (mg %) | 108.26 ± 8.4 | 200.76 ± 55.66 | < 0.001** |

**No significant **Significant*

**Table 2: Comparison of mean P300 latency between control and test groups**

| Parameter | Control --P300 latency (ms) | Test -- P300 latency (ms) | P value |
|---|---|---|---|
| Male | 282.75 ± 9.29 | 319.19 ± 19.13 | <0.001** |
| Female | 285.61 ±10.7 | 323.02 ± 27.29 | <0.001** |
| Total | 283.7 ± 9.69 | 320.94 ± 21.75 | <0.001** |

*** Significant*

**Table 3**: **Comparison of mean P300 amplitude between control and test groups**

| Parameter | Control group P300 amplitude (µV) | Test group P300 amplitude (µV) | P value |
|---|---|---|---|
| Male | 6.12 ± 3.33 | 3.95 ± 1.92 | <0.05** |
| Female | 5 ± 3.17 | 1.53 ± 1.55 | <0.01** |
| Total | 5.75 ± 3.27 | 3.148 ± 2.12 | < 0.01** |

***Significant*

**Table 4: Pearson's coefficient of correlation between P300 latency and various parameters**

| Parameters | FPG | PPPG | Duration of diabetes | Age of control |
|---|---|---|---|---|
| P300 latency | -0.024* | - 0.00033* | 0.157* | 0.032* |

**non-significant*

## DISCUSSION

We aimed to find out cognitive dysfunction in type 2 diabetes by ERP P300. Inspite of taking treatment, patients had poor glycemic control established by their higher glycaemic levels. Central nervous system complications in these patients can lead to diabetic encephalopathy characterized by apoptotic neuronal loss and cognitive decline (Sima *et al.,* 2004). Structural and functional brain changes are observed with both recurrent severe hypoglycemia and hyperglycemia. Alterations in cerebral blood supply, altered neurotransmitter metabolism and metabolic derangements play significant role in pathogenesis of diabetic neuropathy (Kurita *et al.,* 1995; Das *et al.,* 2001; Biessels *et al.,* 1994). Hippocampus, temporoparietel junction and cerebral cortex are main generators of P300 (Polich, 1998; Tarkka *et al.,* 1996). Type 2 diabetic patients had more cortical and subcortical atrophy with more deep white mater lesions and infarcts. These patients were associated with poor glycemic control and cognitive deficits (Manschot SM *et al.,* 2006). Whatever be the etiology, the abnormalities of diabetic metabolism interact with generators of P300 in cerebral cortex to cause delay in cognitive process (Tandon *et al.,* 1999). In our study, we also observed significantly higher P300 latency was in test group than controls (table 2) suggesting cognitive decline. Our observations are similar to many other studies (Alvarenga *et al.,* 2005; Kurita *et al.,* 1995; Tandon *et al.,* 1999; Dey *et al.,* 1997; Cosway et al 2001, Kurita *et al.,* 1996). Whereas Cosway *et al.,* (2001) and Mavioglu *et al.,* (1999) observed non significant increase in P300 latency in diabetics in

comparison with controls. P300 amplitude was significantly reduced in test group, again suggesting impaired cognition (table 3). Whereas many other studies observed reduction of amplitude but it was not significant (Alvarenga *et al.,* 2005; Cosway et al 2001; Mavioglu *et al.,* 1999). As there was insignificant correlation between P300 latency and age of control (table 4) similar to study by Dey *et al.,* (1997) suggesting thereby no relation between them whereas Kurita *et al.,* (1995) and Kurita *et al.,* (1996) found significant correlation. This difference in opinion may be due to difference in sample (number of control) and their age. A larger sample can give more specific result. There was no significant correlation between P300 latency and duration of diabetes as shown in the table 4. Many studies observed similar results (Kurita *et al.,* 1995; Tandon *et al.,* 1999; Dey *et al.,* 1997; Kurita *et al.,* 1996). This can be explained on the basis that cognitive dysfunction occurs during earlier course of disease due to uncontrolled metabolism and this dysfunction does not depend on recent metabolic derangement (Kurita *et al.,* 1995). There were no significant correlations between P300 latency and FBS or PPBS suggesting that current glycemic levels don't affect P300 latency (table 4) similar to many studies (Kalmijn *et al.,* 1995; Tandon *et al.,* 1999; Cosway et al 2001; Kurita *et al.,* 1996). This fact was supported by Mooradian *et al.,* (1988) when they observed that the intravenous administration of glucose (acute hyperglycemia) had no effect on P300 latency in non diabetic subjects. Whereas Alvarenga *et al.,* (2005) demonstrated that reduced glycemic levels in diabetic patients were associated with increased P300 latency and reduction of P300 amplitude. This CNS dysfunction was explained on the fact that nervous tissue is glucose dependent and stable blood glucose levels are required for ideal functioning of CNS.

As all diabetic patients included in present study did not show any CNS symptoms as well as they had a minimum of 5 years of diabetes, so we can say that electrophysiological changes depicting cognitive dysfunction starts few years before appearance of any CNS symptom and this observation was in concordance with study conducted by Pozzessere et al (1988). Thus ERP P300 can be very useful in detecting subclinical cognitive decline early in course of diabetes.

***Conclusion***

Cognitive dysfunction should be recognized as a definite complication of type 2 diabetes. ERP P300 can easily detect cognitive decline before appearance of any neurological symptoms and signs so it should be included in routine diagnostic armamenterium to find out any subclinical cognitive decline early in course of diabetes.

**REFERENCES**

**Alvarenga KF, Duarte JL, da Silva DPC, Agostinbo-Pesse RS, Negrato CA and Costa OA (2005).** Cognitive P300 potential in subjects with diabetes mellitus. *Brazilian Journal of Otorhinolaryngology* **71**(2) 202-207.

**Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW and Gispen WH (1994).** Cerebral function in diabetes mellitus. *Diabetologia* **37** 643-650.

**Cosway R, Strachan MWJ, Dougall A, Frier BM and Deary IJ (2001).** Cognitive function and information processing in type 2 diabetes. *Diabetic Medicine* **18** 803-810.

**Das T, Kundu S, Mazumdar AK and Mukhopadhyay SC (2001).** Studies on central nervous system function in diabetes mellitus. *Journal of the Indian Medical Association* **99**(2) 84-89.

**DeGiorgio CM, Rabinowicz AL and Gott PS (1993).** Predictive value of P300 event related potentials compared with EEG and somatosensory evoked potentials in non traumatic coma. *Acta Neurologica Scandinavica* **87** 423-427.

**Dey J, Misra A, Desai NG, Mahapatra AK and Padma MV (1997).** Cognitive function in younger type II diabetes. *Diabetes Care* **20**(1) 32-35.

**Goodin D, Desmedt J, Maurer K and Nuwer MR (1994).** IFCN recommended standards for long latency auditory event related potentials. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology* **91** 18-20.

**Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL and Venkat KM (2000).** Is diabetes associated with cognitive impairment and cognitive decline among older women? *Archives of Internal Medicine* **160** 174-180.

**Kalmijn S, Feskens EJ, Launer LJ, Stijnen T and Tromhout D (1995).** Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* **38**(9) 1096-1102.

**Kurita A, Katayama K and Mochio S (1996).** Neurophysiological evidence for altered higher brain functions in NIDDM. *Diabetes Care* **19**(4) 361-364.

**Kurita A, Mochio S, Isogai Y (1995).** Changes in auditory P300 event-related potentials and brainstem evoked potentials in diabetes mellitus. *Acta Neurologica Scandinavica* **92** 319-323.

**Manschot SM, Brands AMA, Grond JV, Kessels RPC, Algra A and Kappelle J (2006)**. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes* **55** 1106-1113.

**Mavioglu H, Ozmen B, Yilmaz H and Karaca S (1999).** Cognitive functions and P300 in type II diabetic patients. *Journal of Neurological Sciences (Turkish)* [online] **16**(2). Available from: http://med2.ege.edu.tr/~norolbil/1999/NBD03499.html [Cited on: Jan 20, 2010].

**Mooradian AD, Perryman K, Fitten J, Kavonian GD and Morley JE (1988).** Cortical function in elderly non – insulin dependent diabetic patients: Behavioral and electrophysiologic studies. *Archives of Internal Medicine* **148** 2369-2372.

**Polich J (1998).** P300 clinical utility and control of variability. *Journal of Clinical Neurophysiology* **15**(1) 14-33.

**Pozzessere G, Rizzo PA, Valle E, Mollica MA, Meccia A and Morano S (1988).** Early detection of neurological involvement in IDDM and NIDDM: Multimodel evoked potentials versus metabolic control. *Diabetes Care* **11** 473-480.

**Sadock BJ and Sadock VA (2007).** Contributions of Psychosocial Sciences. In: Kaplan & Sadock's Synopsis of psychiatry, behavioral sciences / clinical psychiatry. 10th edition New Delhi, Lippincott Williams and Wilkins Pvt. Ltd., Philadelphia 133-177.

**Sima AAF, Kamiya H and Li ZG (2004).** Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. *European Journal of Pharmacology* **490** 187-197.

**Tandon OP, Verma A, Ram BK (1999).** Cognitive dysfunction in NIDDM: P3 event related evoked potential study. *Indian Journal of Physiology and Pharmacology* **43**(3) 383-388.

**Tarkka IM, Micheloyannis S, Stokic DS (1996).** Generators for human P300 elicited by somatosensory stimuli using multiple dipole source analysis. *Neuroscience* **75**(1) 275-287.