International Journal of Health Research and Medico-Legal Practice

RESEARCH PAPER

Assessment of event-related potential P300 amongst people with type-2 diabetes and normal individuals

Vijayadas[1], Saha S[2], Preethi BL [3], Kalra P[4]

***Address for Correspondence**:*
[1]Associate Prof Physiology
Email: drvijayadas@gmail.com
*[2]Medical Officer (**Corresponding Author**)*
Department of Physiology
Agartala Government Medical College & GBP Hospital
***Mobile**: +918892698609*
***Email**: satabdiphysio@gmail.com*
Agartala, Tripura-799005
[3]Associate Prof of Physiology
[4]Professor of Endocrinology
Ramaiah Medical College

***Article received**: 14-01-2022*
***Accepted**: 16-02-2022*
***Editorial approval**: 23-06-2022*
***Checked for plagiarism**: Yes*
***Peer-reviewed**: Double-blinded*
***Peer review comments**: Four*
***Editor who approved**: Dr Kahua Das, MD*

ABSTRACT

***Background and aims**: Type-2 diabetes mellitus (DM) is a complex metabolic disorder that has a detrimental effect on almost all human body systems. This study assessed and compared the cognitive function of normal subjects and individuals with type-2 diabetes. **Material and methods**: The study included 15 type-2 diabetics and 15 healthy controls between 20-50 years. P300 was recorded using the standard auditory odd-ball paradigm from the vertex (Cz&Pz) in response to stimuli presented through headphones. The peak latencies of P300 of target stimuli (rare) were calculated. **Results**: P300 latencies were significantly prolonged in the case of type2 diabetes mellitus compared to normal individuals. With the increase in HbA1c level, P300 latencies were increasing. **Conclusion**: An increase in latencies of P300 indicates the presence of a cognitive decline in type-2 diabetics. Our study showed an early onset of cognitive decline, which increased with increasing HbA1c levels.*

***Keywords**: Type 2 diabetes mellitus; cognition.*

***Cite this article**: Vijayadas, Saha S, Preethi BL, Kalra P. Assessment of event-related potential P300 amongst people with type-2 diabetes and normal individuals.Int J Health Res Medico Leg Prae 2022 Jan-June;8(1):36-40. Doi: 10.31741/ijhrmlp.v8.i1.2022.9*

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder. It hampers the normal functioning of almost all the organ systems of the human body. According to the International Diabetes Federation, the number of people with diabetes worldwide will rise to 552 million by 2030 from the 366 million people who had diabetes in 2011.[1]

Type-2 DM is the predominant form of diabetes which involves almost 90% of cases worldwide. The overall life expectancy of diabetics is less than those without diabetes because of the complications of diabetes. All forms of diabetes are associated with microvascular and macrovascular complications. These can lead to accelerated cognitive decline and an increased risk of dementia.[2]

In diabetics, hyperglycaemia, increased free fatty acids, and insulin resistance initiates molecular mechanisms that alter blood vessels' normal function and structure. Atherosclerosis, altered vascular flow, inflammation of blood vessels and altered glucose metabolism lead to neuron degeneration and cognitive decline in the diabetic state. Clinical and animal data indicate that amount and duration of hyperglycaemia

are the two essential determinants of diabetic complications. Several studies have shown poorer cognitive performance and faster cognitive decline in people with diabetes than those without the disease.[3-5]

Most of these findings were based on studies done on elderly subjects and patients with a long duration of diabetes. Type 2 DM is no longer considered a disease of the elderly. Incidence increases in younger individuals because of the interrelation between diabetes and obesity. Cognitive decline in the younger age group is a matter of concern as cognition is associated with goal-directed behaviour and helps the individual adjust to changing environmental needs. Cognitive decline in the younger age group can lead to poorer performance in educational and professional fields. Very few researches have been done to study the effect of type 2 DM on cognition in the younger age group with the duration of diabetes less than five years. Event-related potentials (ERP) are the electrical potentials recorded in the scalp associated with specific sensory, perceptual, cognitive or motor events. P300 is a frequently investigated event-related potential (ERP) that occurs at about 300ms following task-related stimuli. The stimuli can be given either in auditory, visual or somatosensory. It occurs maximum over the midline, central and parietal region. P300 latency is an index of processing time required before response generation.[6]

It is a measure of neural activity underlying the process of cognitive functions. It is negatively correlated with mental function in normal subjects, with shorter latency associated with higher cognitive function. It is prolonged in various neurological, psychiatric disorders and even dementia. Our study recorded P300 latency to assess cognitive function in the early stage of type 2 DM.

MATERIAL AND METHODS

Fifteen type-2 diabetic patients from the Department of Endocrinology, MS Ramaiah Hospital, were included as cases, and 15 age-matched controls were taken from the neighbourhood. The study was undertaken between October 2014 and September 2015. The study group comprised male and female patients with type 2 diabetes mellitus in 20-50 years. The Control group included age, sex, and education-matched healthy individuals. Individuals with a past or present history of psychiatric and neurological disorder, history of ear and eye disease, chronic alcoholics and chronic smokers, patients with thyroid and renal disorder, and patients on drugs that may alter the psychomotor function were excluded from the study. Ethical clearance was obtained from the authority. Testing procedures and protocols were explained in detail to the subjects. Written consent was obtained from the cases and controls. The study subjects were evaluated by general history, clinical examination, and blood HbA1c level. Cognitive function was tested by event-related potential P300.

Electrode placement: The subjects were seated comfortably in a semi-darkened, acoustically shielded, air-conditioned room. The electrode placement sites were cleaned with spirit. Ag/AgCl disc electrodes were placed with conductive paste at Fz, Cz, Pz, C3, P3, A1 & A2 of the 10-20 International system, as shown in **Figure 1**. FPz was taken as the grounding electrode, and A1 & A2 were used as reference electrodes. All the electrodes were connected to a junction box, and skin-to-electrode impedance was kept at < 5KW.

P300: ERP P300 was recorded using the Nihon Kohden Neuropack (MEB 2200 Version 03.02), as shown in **Figure 2**. P300 recording consisted of stimulus presentation via an odd-ball paradigm in which an unexpected infrequent stimulus was interspersed among frequent stimuli. The procedure was explained to the subjects. They were familiarised with the stimuli & requested to remain alert and awake during the process. The subject presented 300 stimuli as a sequence of two different sound stimuli. One frequently occurred (frequent stimulus /non-target) 240 times and the other infrequently (rare stimulus/target) 60 times. The frequency of the frequent stimulus was 750 Hz, and that of the rare stimulus was 2000Hz. The subjects were asked to press a button whenever they heard the target sound. The evoked responses to the rare stimuli were filtered with a bandpass of 1-30 Hz and averaged. Samples contaminated with artefacts were auto discarded. A high pass setting of 0.01 Hz and a low pass setting of 100 Hz was employed. The positive wave appeared about 300 ms after the stimulus was marked as P300, and the latency was measured at the point of maximum amplitude. Peak latencies of P300 were also compared among the groups.

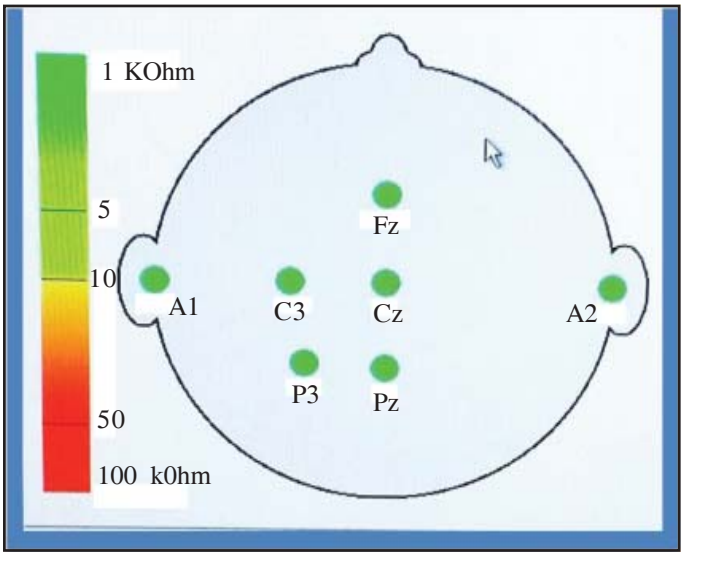

Figure 1 Electrode placement

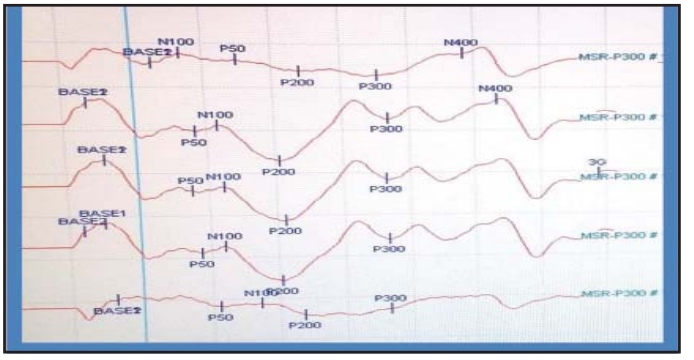

Figure 2 P300 waveform

Statistical Analysis:

Statistical analysis was done using SPSS 20. All parameters were summarized using mean and standard deviation. The student's t-test was used to compare mean differences in all the parameters between the two groups. Pearson's correlation was used to assess the correlation between HbA1c level and P300 latencies.

RESULTS

The study was conducted on a group of 15 healthy individuals & 15 type2 diabetic patients. The study groups were similar based on age (P >0.05). The mean age of the controls was 27.80 ± 7.10 years, and those with diabetes were 31.73 ± 3.84 years. The study groups had significantly different HbA1c levels reflecting their respective blood glucose level. The mean HbA1c level in people with diabetes was 7.2 ± 0.676 %, as shown in **Table 1** and **Figure 3**.

Table1 Baseline characteristics of Group I (controls) & Group II (Type 2 diabetics)

Parameters	Controls (n=15)	Diabetics (n=15)	p value
Age (years)	27.80 ± 7.10	31.73 ± 3.84	0.07
Duration of diabetes (yrs)	0	2.73 ± 1.33	0.000*
HbA1c (%)	5.13 ± 0.352	7.2 ± 0.676	0.000*

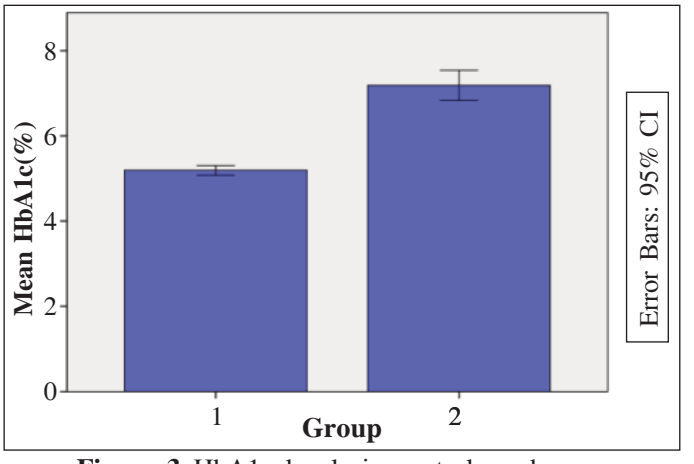

Figure 3 HbA1c levels in controls and cases

P300 latencies were significantly prolonged in the case of type 2 diabetes mellitus compared to normal individuals. P300 latencies of cases and controls are summarised in **Table 2** and **Figure 4**.

Table 2 P300 latencies of Group I(controls), Group II(Type2 diabetics)

Parameters	Controls (n=150)	Diabetics (n=15)	p-value
Fz-AR P300	340.25 ± 52.84	372.53 ± 47.98	0.047*
Cz-AR P300	317.25 ± 41.70	377.6 ± 37.23	0.001*
Pz-AR P300	316.5 ± 35.31	371.53 ± 37.26	0.001*
C3-AR P300	307.25 ± 33.82	381.53 ± 38.03	0.000*
P3-AR P300	313.41 ± 36.51	377.8 ± 40.24	0.000*

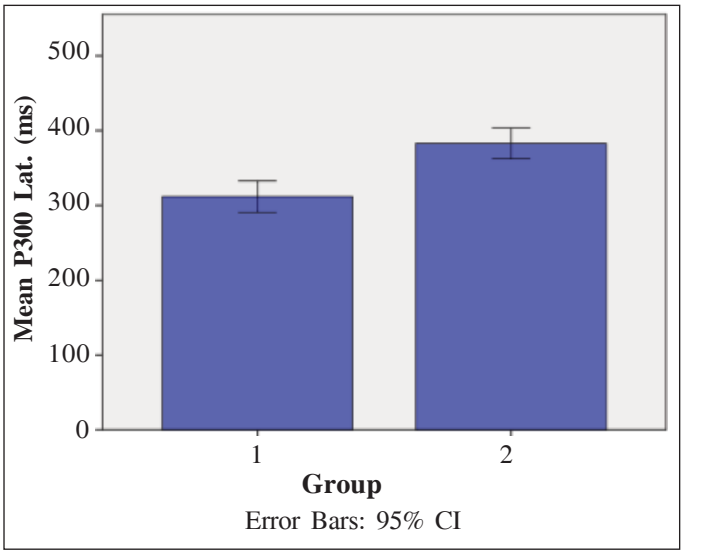

Figure 4 Mean P300 latencies in cases and controls

Pearson's correlation showed a strong positive correlation (r=0.829) between HbA1c levels and P300 latencies which were statistically significant (p=0.001), as shown in **Figure 5**.

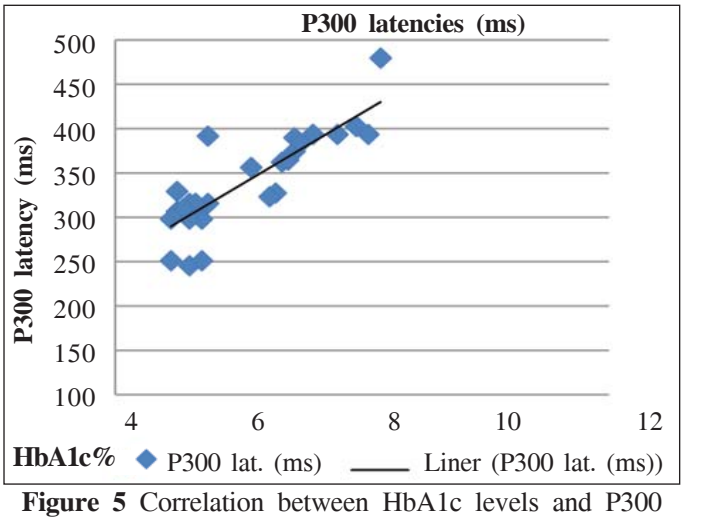

Figure 5 Correlation between HbA1c levels and P300 latencies in cases

DISCUSSION

P300 event-related potential (ERP) measures the speed of neural events related to attention and short-term memory.[7] Different areas of the brain involved in the generation of P300 are the inferior parietal lobule, frontal lobe, hippocampus, medial temporal lobe, insular cortex and other limbic structures. P300 latency increases systematically as cognitive capability decreases.[8] It is prolonged in ageing, dementia and other neurodegenerative diseases. Our study found that P300 latencies were significantly prolonged in type 2 diabetes mellitus, similar to other studies' findings.[9-10] We analyzed the cognitive function of people with type 2 diabetes, where diabetes was less than five years. The age group was 20-50 years, much less than in other studies.[11] Munshi M et al. showed similar findings in their study, but the duration of diabetes was much longer.[12] We observed that cognitive decline is present even in the early stages of DM. This supports the finding of the study done by Carla Luis et al.[13]

Another important finding of our study was the negative correlation between HbA1c level and cognitive function. Cognitive decline increased with increasing HbA1c levels. This is consistent with previous work that says glycosylated haemoglobin can predict cognitive decline.[14] The Springer RR et al. study showed that in non-diabetic, non-demented elderly subjects, an increase in HbA1c is associated with concurrent cognitive decline.[15]

Hyperglycaemia leads to the formation of the advanced glycation end product (AGEs), which can cause degeneration of neurons, glial cells and myelin sheath. AGE-mediated brain injury may be a cause of the cognitive decline. Increased blood glucose level leads to the activation of Protein kinase C, which can also lead to atherosclerotic changes in the blood vessels, retard the blood flow to the brain. Microvascular and macrovascular complications are well known in diabetes mellitus. Hyperglycaemia is also proposed to cause end-organ damage by increasing the generation of reactive oxygen species. The combined effect of all these factors is neuronal damage in the brain. In the presence of neuronal damage, information processing may be delayed, leading to impaired cognitive function.

Other likely mechanisms of cognitive dysfunction in T2DM are atrophy in the hippocampus and amygdala[16]and insulin resistance. The mechanism by which insulin resistance causes cognitive decline is unclear. The impairment of neurotransmission, memory formation and central cholinergic activity contribute to cognitive decline.[17]

The findings of our study, that is, the presence of a cognitive decline in the early stage of type 2 DM, emphasize prompt management of diabetes and controlling HbA1c level even before any clinical signs and symptoms appear. All type 2 diabetic patients should be screened for cognitive decline and other neurological examinations at the time of diagnosis and regularly after that to improve their quality of life as cognitive decline may affect their educational and professional performance.

Limitations: One limitation of our study is the small sample size. Also, unknown and sub-clinical complications, which are unaccounted for, may contribute to cognitive function.

CONCLUSION

An increase in latencies of P300 indicates the presence of a cognitive decline in type-2 diabetics. Our study shows an early onset of cognitive decline, which increased with increasing HbA1c levels.

Conflict of interest: None declared.

Funding: The work was not supported by any funding agency.

Acknowledgement: We are thankful to the whole Dept. of Physiology and Dept. of Endocrinology, Mrs Radhika Kunnavil, Lecturer cum Statistician in the Dept. of Community Medicine, Dr Arun Kumar M, Assistant professor of in the Dept. of Physiology; MS Ramaiah Medical College, Bangalore, for their valuable inputs.

Ethical clearance: Taken from the ethics committee of Ramaiah Medical College.

REFERENCES

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311-321. Doi: 10.1016/j.diabres.2011.10.029
2. Saczynski JS, Jónsdóttir MK, Garcia ME, Jonsson PV, Peila Rita, EiriksdottiretGudny at al. Cognitive Impairment: An Increasingly Important Complication of Type 2 Diabetes. Am J Epidemiol 2008;168(10):1132-9. Doi: 10.1093/aje/kwn228
3. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol2006;5:64-74. Doi: 10.1016/S1474-4422(05)70284-2
4. Exalto LG, Whitmer RA, Kappele LJ, Biessels GJ. An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol 2012;47:858-64. Doi: 10.1016/j.exger.2012.07.014
5. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819-28. Doi: 10.1016/S1474-4422(11)70072-2
6. Singh M, Kumar N, Sood S. Study of effect of type 2 diabetes mellitus on cognitive functions by event-related

potential p300. ISSN. 2013;3(1):24-8.

7. Hazari MAH, Reddy BR, Uzma N, Kumar BS. Cognitive impairment in type 2 diabetes mellitus, Int J Diab Mellitus 2011. Doi: 10.1016/j.ijdm.2011.01.001
8. Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 2000;38(1):3-19. Doi: 10.1016/s0167-8760(00)00127-6
9. Mochizuki Y, Oishi M, Hayakawa Y, Matsuzaki M, Takasu T. Improvement of P300 latency by treatment in non-insulin-dependent diabetes mellitus. Clin Electroencephalogr 1998;29(4):194-6. Doi: 10.1177/155005949802900413
10. Alvarenga KdeF, Duarte JL, da Silva DPC, Agostinho-Pesse RS, Negrato CA, Costa OA. Cognitive P300 potential in subjects with diabetes mellitus. Rev Bras Otorrinolaringol 2005;71(2):202-7. Doi: 10.1016/s1808-8694(15)31311-2
11. Jane S. Saczynski, Marý´a K. Jo'nsdo' ttir, Melissa E. Cognitive Impairment: An Increasingly Important Complication of Type 2 Diabetes. Am J Epidemiol 2008;168:1132-9. Doi: 10.1093/aje/kwn228. Epub 2008 Oct 3
12. Munshi M, Grande L, Hayes M, Ayres D, Suhl E, Capelson R et al. Cognitive Dysfunction Is Associated With Poor Diabetes Control in Older Adults. Diabetes Care 2006;29:1794-9.
13. Ruis C, Biessels GJ, Gorter KJ, Donk M, Kappele LJ, Rutten G E. Cognition in the Early Stage of Type 2 Diabetes. Diabetes Care 2009;32:1261-5. Doi: 10.2337/dc06-0506
14. Yaffe K, Blackwell T, Whitmer RA, Krueger K, Connor EB. Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging 2006 Jul-Aug;10(4):293-5.
15. Springer RR, Moshier E, Schmeidler J, Godbold J, Akrivos J, Rapp M, et al. Changes in Glycemic Control are Associated with Changes in Cognition in Non-Diabetic Elderly. J Alzheimers Dis 2012;30(2):299-309. Doi: 10.3233/JAD-2012-120106
16. Den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46(12):1604-10. Doi: 10.1007/s00125-003-1235-0
17. Christopher T. Kodl, Elizabeth R. Seaquist. Cognitive dysfunction and diabetes mellitus. Endocr Rev. Jan 2008;29(4):494-511. Doi: 10.1210/er.2007-0034.