Original Article

Study of Neurocognitive Function in Type 2 Diabetes Mellitus Patients Using P300 Event-Related Potential

Annals of Neurosciences
27(3-4) 98–103, 2020

DOI: 10.1177/0972753120966824
journals.sagepub.com/home/aon
SAGE

Swaminathan Anandhalakshmi[1], Ramanathan Rajkumar[2], Karuppannan Arulmurugan[3], Janardanan Kumar[4], and Manickam Thirunavukarasu[2]

Abstract

Background: Diabetes mellitus is the most prevailing metabolic disease. It causes structural and functional alterations in several organs, including the central nervous system. Altered glucose metabolism, atherosclerosis, and inflammation of blood vessels are seen in diabetes. This may lead to neuronal degeneration and decline in cognition. Event-related potential P300 can detect cognitive decline before the emergence of obvious neurological manifestations.
Objective: The aim of this study is to assess and compare the P300 latencies in subjects with type 2 diabetes mellitus and in nondiabetic subjects and to determine the influence of type 2 diabetes mellitus on cognitive functions.
Methods: In this study our sample size was 248 subjects, with type 2 diabetes mellitus patients (n = 124) and healthy controls (n = 124) between the age group of 31 and 60 years. This cross-sectional comparative study was conducted at SRM Medical College Hospital and Research Centre. The subjects were evaluated by a structured interview and they were assessed with a general health questionnaire to rule out any subpsychiatric illness. Fasting and postprandial blood glucose, HbA1c level, lipid profile, and creatinine were estimated. P300 amplitude and peak latencies were recorded using the standard auditory oddball paradigm.
Results: The latencies of P300 were significantly increased and the amplitude of P300 was significantly reduced in the diabetic group when compared to the control group ($P < .001$). P300 latency has a positive correlation with the HbA1c levels (r = 0.136) and the duration of diabetes (r = 0.231).
Conclusion: Prolongation of P300 latencies and the decreased amplitude in diabetic subjects may suggest the existence of a cognitive decline in individuals with type 2 diabetes compared to healthy individuals.

Keywords

Event-related potential P300, type 2 diabetes mellitus, cognitive function, serum HbA1c

Introduction

Diabetes mellitus is one of the leading health care problems in India with an estimated 66.8 million people suffering from the condition, thereby representing the largest number in any country in the world.[1] Currently, diabetes mellitus is one of the most prevalent chronic-degenerative diseases. Most of the complications of diabetes mellitus are chronic and may affect multiple organs such as eyes, kidney, cranial nerves, peripheral nerves, and the heart. Cognitive function may also to be affected in subjects with diabetes mellitus and this concomitant cognitive dysfunction generally goes unnoticed and less studied.

Cognitive impairment in diabetes in terms of processing speed and attention was observed in patients with diabetes mellitus especially during hyperglycemia.[2,29] It may dramatically affect their ability to learn. In the present scenario diabetes-related complications can be reduced if patients are able to

[1] Department of Physiology, All India Institute of Medical Sciences, Kalyani, West Bengal, India
[2] Department of Psychiatry, SRM Medical College, Kattangulathur, Chennai, India
[3] School of Public Health, SRM University, Kattangulathur, Chennai, India
[4] Department of General Medicine, SRM Medical College, Kattangulathur, Chennai, India
Corresponding author:
Swaminathan Anandhalakshmi, Department of Physiology, All India Institute of Medical Sciences, Kalyani, West Bengal 741235, India.
E-mail: dranandhalakshmismd@gmail.com

maintain good glycemic control, which requires a more complex treatment regimen and better self-care skills to manage the disease safely. Self-care skills include healthy eating, being physically active, monitoring of blood sugar, compliant with medications, good problem-solving skills, healthy coping skills, and risk-reduction behaviors.[3]

Cognitive dysfunction reduces the ability of the subjects to implement these complex regimens. Medical care in the absence of adequate self-care is rarely effective for chronic illnesses. Self-care in diabetes has important clinical and public health implications. Thus, 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 measures for this condition.

Several studies have revealed an electrophysiological evidence of cognitive dysfunction in diabetes, even in the absence of clinical signs of central nervous system damage.[4–9] Additionally, P300 has been shown to be more sensitive in detecting cognitive deficits than psychometric tests in type 2 diabetes mellitus.[9] Cognitive P300 potential has been used as an objective procedure to determine brain cognitive function, and the right tool to check the effect caused by glycemic changes in the hippocampus region.[7]

However, conflicting results have been reported regarding the correlation of ERPs abnormalities with clinical parameters in diabetics.[4–9] A few other studies suggest that decline in cognitive function correlated to hyperglycemia was seen in type 2 diabetes mellitus patients[9,10] and cognitive function had been improved by controlling blood glucose tested by the noninvasive tool cognitive P300.[11]

There is also paucity of data on ERP abnormalities in individuals with diabetes mellitus type 2 in Indian scenario, especially from South India which differs in dietary habits. If there is any association between diabetes mellitus and cognitive impairment, identifying the impairment in the early stage and providing treatment may alleviate its consequences which can provide an independent and good quality of life to diabetic subjects. Therefore, the present study was carried out to explore the impact of type 2 diabetes mellitus on cognitive functions by evaluating event-related potential P300 (ERP P300) in patients with type 2 diabetes mellitus in comparison with the control group and to examine the relationship of P300 with the duration of disease and short-term metabolic control.

Materials and Methods

This is a cross-sectional comparative study conducted at SRM Medical College Hospital and Research Centre, Tamil Nadu.

Selection of Sample

124 subjects with type 2 diabetes mellitus (according to American Diabetes Association (ADA) criteria) in the age group of 31 to 60 years attending the out-patient Department in Diabetology were included in the study. 124 age and sex matched normoglycemic individuals were included as a comparison group.

Patients with history of neurological disease, psychiatric illness, head injury, sleep disorders, peripheral vascular diseases, dementia, stroke, hypertension, dyslipidemia, mental retardation, and history of substance abuse were excluded from the study. This study was approved by the institutional ethical committee. Written informed consent was taken from the subjects after proper explanation. The participants were informed that they were free to withdraw from the study at any stage.

Process of Assessment

The patients and the controls were subjected to a structured interview in the out-patient department. We used the general health questionnaire (GHQ 28) to screen the participants for subpsychiatric illness and if present were excluded from the study. Details about age of onset of diabetes, diabetes duration, and treatment for diabetes were recorded. The participants have undergone the following tests: fasting and postprandial blood sugar, glycated hemoglobin (HbA1c), lipid profile, and creatinine. They underwent ENT examination and those with normal hearing were included.

The Event-Related Potential

Event-Related Potentials (ERPs) are good indices which objectively quantify the level of cognitive impairment in comparison to other psychometric tests used for evaluating cognitive functions.[12–14] The ERPs give an idea regarding the timeline of information processing involved in expectancy, attention, cognition search, decision-making, and memorization.[15] ERP is the extrinsic recording of the internal electrical activity of the underlying brain structure emerging from a stimulus bound activity. This is documented by using an unconventional model in which the individual is vigilant and consciously discriminates an auditory stimulus from a cluster of other auditory stimuli. ERPs consist of an array of positive waves and negative waves that originate above the brainstem.

The P300 is a positive potential that happens almost 300 milliseconds (ms) subsequent to the stimulus presented, requiring discrimination, counting, or cognitive processing by the participant.[16,17] Investigators mostly depend on the measurement of the P300 to examine ERP, especially concerned with decision-making. This waveform can be used as a measure of the effectiveness of different treatments on cognitive function because cognitive impairment is often

associated with modification in the P300.[18] For this reason scientists have supported its use as a clinical marker. There is a vast range of applications for the P300 in scientific research such as study of depression, drug addiction, and anxiety disorders.[19]

P300 latency is an indicator of processing time needed before producing a response and so it is a precise temporal measure of neuronal functioning fundamental to the process of immediate memory.[20] The shorter latencies of P300 are associated with superior cognitive performance when compared to prolonged latency. Thus, P300 latency has a negative correlation with intellectual functions in normal subjects. P300 amplitude can be perceived as a measure of neuronal processing that indicates the handling of incoming information when it is included in memory representation of stimulus and the situation in which the stimulus takes place.[21]

Recording of ERP P300

In this study, the P300 ERP was recorded for all the subjects after informing about the nature of procedure. The subjects were not allowed to consume caffeine- and tannin-containing drinks ten hours before the test and until the completion of the test. The ERP recording was done in the morning hours between 9 am and 11 am, one hour after a light breakfast. This electrophysiological study for evaluating P300 variables was done using microprocessor-based testing equipment which included a dedicated software: RMS EMG EP MARK II (Recorders and Medicare Systems Pvt. Ltd, Chandigarh, India). A standard setting was used while doing the electrophysiological study. Disc type of Ag/AgCl electrodes were used to pick up the evoked responses from scalp. They were placed on the scalp after appropriate skin preparation by cleansing, degreasing, and abrading. The conducting jelly was gently applied on to the area for securing adequate and steady electrical connection. The active electrode on the vertex was termed as Cz, and A1 and A2 were the two reference electrodes attached to the left and right mastoids, respectively. The ground electrode labeled as Fz was attached to the forehead. All electrodes were connected to a junction box. Skin-to-electrode impedance was monitored and was kept below 5 Kohms. The noise was below 0.5 μV.

The study was conducted in a climate-controlled and soundproof room after the subjects were made to relax. Patients were instructed to keep their eyes closed, avoid eye movement to reduce artifact. ERP wave pattern was recorded in the context of a standard auditory oddball paradigm. The stimuli were of two types: target (rare tone) stimuli and nontarget (frequent tone) stimuli. The subjects underwent two tone auditory discrimination task delivered using oddball paradigm. Two types of tones 2000 Hz (target stimulus) and 750 Hz (nontarget) were delivered through earphones at 75 dB with a rate of 1.1 per second. Rare stimulus was randomized to occur at 20% which means that out of 100 stimuli, 80 were frequent stimuli and 20 were rare stimuli. They were asked to identify and count rare stimulus. N2 and P3 recordings were obtained from Cz on the presentation of high-pitched infrequent click sounds in a train of low-pitched frequent sound.[22] One or two trial sessions were given till the subjects were able to discriminate target and nontarget stimuli. Letters P and N are used to denote positive and negative waves, respectively. There are two positive waves P2 and P3, and two negative waves N1 and N2. Labeling is based on their average latency, that is, P300 appears around 300 ms after stimulus. The measurement of P300 latency is up to the point of maximum P300 amplitude. Sweep width (in msec) is 200 ms/D and the number of sweeps averaged is 500.

The signals were captured by electrodes, and then filtered, amplified, averaged, and displayed on the screen. Trials with significant artifacts, including eye-movements, muscle artifacts, and skin potentials were manually excluded before generating the averaged ERP waveforms.

Statistical Analysis

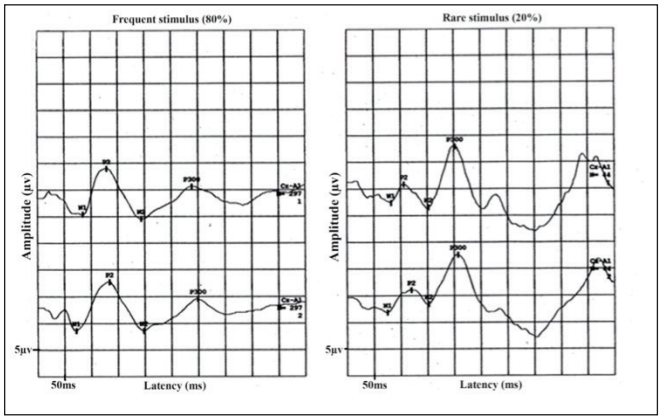
The data were entered in an Excel sheet. Statistical analysis was done using SPSS software. Data were presented as mean $\pm$ standard deviation. The tests used were Student's *t* test and Pearson correlation tests. *P* value of $< .05$ was considered statistically significant.

Table 1. Comparison of Physical Characteristics Between Diabetics and Controls

Parameters	Diabetics (*n* = 124) Mean + SD	Controls (*n* = 124) Mean + SD	*P* Value
Age in years	51 ± 7.8	50 ± 5.6	.231
Height	154 ± 8.2	159 ± 7.2	.516
Weight	63.48 ± 8.4	61.12 ± 8.7	.10
BMI	26.72 ± 3.78	25.76 ± 4.23	.273

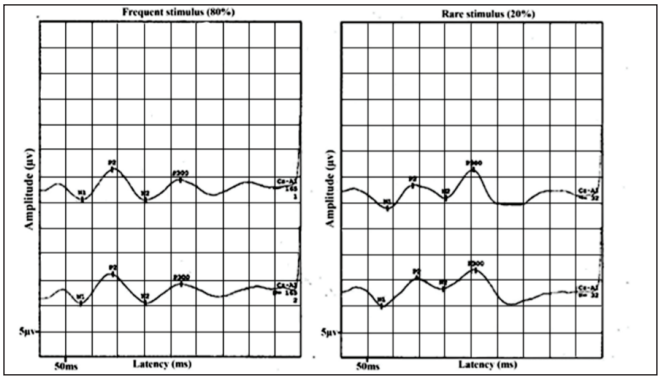
Abbreviations: SD, standard deviation; BMI, body mass index.

Figure 1. Event-Related Potential P300 Waveform Recorded in Response to Frequent Stimuli and Rare Tone Stimuli Obtained from Control



Note. The ERP latency was shown in horizontal axis and amplitude in vertical axis.

Figure 2. Event-Related Potential P300 Waveform Recorded in Response to Frequent Stimuli and Rare Tone Stimuli Obtained from Diabetic Subject



Note: The ERP latency was shown in horizontal axis and amplitude in vertical axis.

Table 2. Comparison of Event-Related Potentials Between Diabetics and Controls

Parameters	Diabetes (n = 124) Mean ± SD	Controls (n = 124) Mean ± SD	t Value	P Value*
P300 latency (ms)	301.18 ± 22.88	282.48 ± 28.70	5.674	<.001*
P300 amplitude (μV)	6.53 ± 9.33	10.08 ± 8.42	-2.135	.034*

Abbreviation: SD, standard deviation.

Note: *P < .05 indicates statistical significance.

Table 3. Comparison of Event-Related Potentials Between Diabetic Males and Females

Parameters	Diabetic Males (n = 46) Mean ± SD	Diabetic Females (n = 78) Mean ± SD	t Value	P Value
P300 latency (ms)	296.76 ± 31.45	290 ± 22.09	1.201	.232
P300 amplitude (μV)	8.17 ± 22	5.56 ± 9.46	0.91	.361

Abbreviation: SD, standard deviation.

Note: *P < .05 indicates statistical significance.

Table 4. Correlation Between Event-Related Potential Parameters, FBS, PPBS, HbA1c, and Duration Diabetes

Parameters		FBS	PPBS	HbA1c	Diabetes Duration
P300 latency (ms)	r value	0.063	0.085	0.136	0.231
	P value	0.319	0.183	0.032*	0.010*
P300 amplitude (μV)	r value	-0.096	-0.060	0.001	-0.056
	P value	0.133	0.346	0.987	0.539

Abbreviations: FBS, fasting blood sugar; PPBS, postprandal blood sugar.
Note: *P < .05 indicates statistical significance; **r value shows significant correlation.

Results

The physical characteristics such as age, height, weight, and body mass index of 124 diabetic patients and 124 controls were summarized in Table 1. Table 1 shows that there is no significant difference in the physical characteristics between the study groups and that they were comparable. Table 2 compares the ERP between the diabetic group and the controls. The mean P300 latency of the diabetic group was 301.18 ± 22.88 and that of the controls was 282.48 ± 28.71 and shows that the peak latencies of P300 were significantly prolonged in the diabetic group when compared to the control group (P < .001). Also, Table 2 shows that the mean amplitude of P300 was 6.53 ± 9.33 for the diabetic group and 10.08 ± 8.42 for the controls. The amplitude of P300 was significantly reduced in diabetic subjects when compared with that of the controls (P = .034).

Table 3 compares the P300 latencies and amplitude between the diabetic males (n = 46) and females (n = 78). The mean P300 latency of the diabetic males was 296.76 ± 31.45 and that of diabetic females was 290 ± 22.09. There was no significant difference in the peak latencies of P300 between diabetic males and females (P = .232). The mean amplitude of P300 was 8.17 ± 22 for the diabetic males and 5.56 ± 9.46 for the diabetic females. There was no significant difference in the amplitude of P300 between diabetic males and females (P = .361).

The correlation between ERP, fasting blood sugar (FBS), postprandal blood sugar (PPBS), HbA1c, and the duration of diabetes were shown in Table 4. P300 latency had a positive correlation with the HbA1c levels and the duration of diabetes. The P300 latency did not have any significant correlation with FBS and PPBS. The P300 amplitude did not have any significant correlation with FBS, PPBS, HbA1c, and duration of diabetes.

Discussion

During the electrophysiological recording of ERP, two types of auditory stimuli such as frequent tone stimuli and rare tone stimuli were given. The ERP wave pattern observed with a frequent and rare tone stimulus of the control is shown in Figure 1 and the ERP pattern with a frequent and rare tone stimulus of diabetic subject is shown in Figure 2. In both the N1 wave is followed by positive P2 followed by negative N2 and positive P300.

In all subjects the rare tone stimuli wave patterns were used for electrophysiological evaluation of P300. The mean amplitude of P300 (rare tone stimuli) component of endogenous cognitive evolved potentials in the control group was 10.08 ± 8.42 μV and the same in diabetic group was 6.53 ± 9.33 μV. As shown in Table 2, the statistical analysis revealed that the mean latency of P300 was significantly prolonged (P < .001) and the mean amplitude of P300 was significantly

decreased ($P < 0.05$) in diabetic patients as compared to the controls. Our results are similar to studies by Hazari et al.[23] and Mohamed et al.[24] who showed prolonged P300 latencies in diabetics.

The areas attributed as generators of P300 include inferior parietal lobe, frontal lobe, hippocampus, medial temporal lobe, insula, and other parts of limbic system.[21,25] According to Tandon et al.,[7] diabetic milieu causes delay in cognitive process by interacting with ERP generators in cerebral cortex. Taking into account the fact that P300 latency reflects the speed of neuronal functions underlying information processing and that P300 amplitude is mirroring with attention and short-term memory, the observed electrophysiological abnormality in our study reflects impairment in attention, memory, and speed of information processing which is indicative of early cognitive impairment in diabetes. Since the incidence of Alzheimer's disease is increasing in diabetics, assessing cognitive function by a non-invasive tool like P 300 is very essential in formulating the preventive and treatment measures.[32-35]

In our study among the diabetics there were 46 males and 78 females. Table 3 compares the event related potential latency and amplitude between the diabetic males and females and there were no significant difference noted between the two.

In our study there were no significant correlations between P300 latency and FBS or PPBS (Table 4) similar to many studies.[7,26,27,30,31] Table 4 shows that P300 latency had a positive correlation with the duration of diabetes and the HbA1c levels. The P300 amplitude had inverse correlation with the duration of diabetes. Our results differ from Nooyens et al.,[28] who in their study had suggested that decline in the speed of cognitive processes is greater during the early stages of diabetes. But the results of Singh et al.[10] and Tandon et al.[7] did not show any significant correlation between P300 latency and duration of diabetes. Our study findings suggest that in poorly controlled diabetics, cognitive processes in the brain were slowed down. Our findings are in concordance with the results of Hissa et al.,[8] who confirmed that there is a significant correlation between P300 cognitive potential and duration of diabetes mellitus. It shows that long-term complications are more significant in the course of this metabolic disorder as it affects neuronal functions. Cognitive impairment does have a large impact on diabetic self-management and abidance to treatment. The identification of presence of subclinical cognitive impairment in diabetic patients is useful while planning treatment strategies for these patients.

Conclusion

In our study, subjects with diabetes mellitus have prolonged P300 latency and reduced amplitude, when compared to the nondiabetic control group and have a significant correlation with the duration of diabetes and the HbA1c levels. These findings suggest the existence of cognitive decline in subjects with diabetes which further correlates with disease duration and metabolic control. Because ERP P300 can be used to detect any subclinical cognitive decline in course of diabetes, it can be included in routine investigations, for early detection, and for appropriate management of diabetes.

Acknowledgments

The authors would like to acknowledge Mrs Thilagavathy Kavin, Assistant Professor, Master of Public Health, SRM Medical College for her valuable help in statistical analysis of the data. The authors also thank Dr P. Venkataraman, Assistant Professor, Medical Research for his support.

Author Contributions

S. A. carried out the experiment and wrote the manuscript with support from R. R.
K. A. verified the analytical methods.
J. K. encouraged Swaminathan Anandhalakshmi to investigate. M. T. supervised the project.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

This study was approved by the institutional ethical committee.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Swaminathan Anandhalakshmi https://orcid.org/0000-0002-6698-9144

References

1. Joshi SR. Diabetes care in India. Annals of Global Health November 1, 2015; 81(6): 830–838.
2. Sommerfield AJ, Deary IJ, and Frier BM. Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. Diabetes Care 2004; 27(10): 2335–2340.
3. American Association of diabetes educators. AADE7 self-care behaviors. Diabetes Educ 2008; 34: 445–449.
4. Pozzessere G, Valle E, de Crignis S, et al. Abnormalities of cognitive functions in IDDM revealed by P300 event-related potential analysis. Comparison with short-latency evoked potentials and psychometric tests. Diabetes 1991; 40(8): 952–958.
5. Mooradian AD, Perryman K, Fitten J, et al. Cortical function in elderly noninsulin dependent diabetic patients. Behavioral and electrophysiologic studies. Arch Intern Med 1988; 148(11): 2369–2372.

6. Mattlar CE, Falck B, Rönnemaa T, et al. Neuropsychological cognitive performance of patients with type-2 diabetes. Scand J Rehabil Med 1985; 17(2): 101–105.
7. Tandon OP, Verma A, and Ram BK. Cognitive dysfunction in NIDDM: P3 event related evoked potential study. Indian J Physiol Pharmacol 1999; 43(3): 383–388.
8. Hissa MN, D'Almeida JA, Cremasco F, et al. Event related P300 potential in NIDDM patients without cognitive impairment and its relationship with previous hypoglycemic episodes. Neuro Endocrinol Lett June 1, 2002; 23(3): 226–230.
9. Alvarenga FK, Duarte JL, Silva DP, et al. Cognitive P300 potential in subjects with diabetes mellitus. Braz J Otorhinolaryngol 2005; 71(2): 202–207.
10. Singh M, Kumar N, Sood S, et al. Study of effect of type 2 diabetes mellitus on cognitive functions by event related potential P300. Int J Basic Appl Med Sci January 2013; 3(1): 24–28.
11. Mochizuki Y, Oishi M, Hayakawa Y, et al. Improvement of P300 latency by treatment in noninsulin-dependent diabetes mellitus. Clin Electroencephalogr October 1998; 29(4): 194–196.
12. Alexander MP and Geschwinal N. Dementia in the elderly. In: ML Albert ed. *Clinical neurology of aging*. New York, NY: Oxford University Press, 1984, 259–276.
13. Katzman R, Terry RD, and Bick KL. *Alzheimer's disease: Senile dementia and related disorders*. New York, NY: Raven Press, 1978, 29–41.
14. Tandon OP and Mahajan AS. Averaged evoked potentials: Event related potentials (ERPs) and their applications. Indian J Physiol Pharmacol October 1999; 43: 425–434.
15. Licht R and Homberg V. An introduction of methodology, psychophysiological significance and clinical application. In: EJ Colon and SL Visser eds. *Evoked potentials manual*. Netherlands: Kluwer, 1990, 327–353.
16. Salisbury DF, Rutherford B, Shenton ME, et al. Button-pressing affects P300 amplitude and scalp topography. Clin Neurophysiol September 1, 2001; 112(9): 1676–1684.
17. Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol October 1, 1992; 9(4): 456–479.
18. Golob EJ, Johnson JK, and Starr A. Auditory event-related potentials during target detection are abnormal in mild cognitive impairment. Clin Neurophysiol January 1, 2002; 113(1): 151–161.
19. Hansenne M. The P300 cognitive event-related potential. I. Theoretical and psychobiologic perspectives. Clin Neurophysiol August 2000; 30(4): 191–210.
20. Goodin D, Desmedt J, Maurer K, et al. IFCN recommended standards for long-latency auditory event-related potentials. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol July 1, 1994; 91(1): 18–20.
21. Tarkka IM, Micheloyannis S, and Stokić DS. Generators for human P300 elicited by somatosensory stimuli using multiple dipole source analysis. Neuroscience September 6, 1996; 75(1): 275–287.
22. Misra UK and Kalita J. *Clinical neurophysiology*. 2nd ed, India: Elsevier, 2006, 401–410.
23. Hazari MA, Reddy BR, Uzma N, et al. Cognitive impairment in type 2 diabetes mellitus. Int J Diabetes Mellitus May 1, 2015; 3(1): 19–24.
24. Mohamed MG, Khedr EM, Ahmed MA, et al. Insulin resistance and cognitive impairment in type 2 diabetes mellitus. Int J Diabetes Res 2019; 2(1): 21–25.
25. Polich J. P300 clinical utility and control of variability. J Clin Neurophysiol January 1, 1998; 15(1): 14–33.
26. Cosway R, Strachan MW, Dougall A, et al. Cognitive function and information processing in type 2 diabetes. Diabet Med October 2001; 18(10): 803–810.
27. Kurita A, Mochio S, and Isogai Y. Changes in auditory P300 event-related potentials and brainstem evoked potentials in diabetes mellitus. Acta Neurol Scand October 1995; 92(4): 319–323.
28. Nooyens AC, Baan CA, Spijkerman AM, et al. Type 2 diabetes and cognitive decline in middle-aged men and women: The Doetinchem cohort study Diabetes Care September 1, 2010; 33(9): 1964–1969.