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Assessment of Cognition in Prediabetics in a Tertiary Care Hospital of Tamil Nadu - A Cross-Sectional Study

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ABSTRACT

Introduction: Prediabetes is more common in young adults. The worldwide prevalence of Impaired Glucose tolerance (IGT) was found to be 343 million (7.8%). In India the prevalence of Pre-diabetes is found to be 10.6%. Cognition refers to all the mental activities involved in receiving information, comprehending it, sorting, retrieving, and using it. Cognitive decline is one of the neurological complications of prediabetes.
Aim: To evaluate whether cognition is impaired in the pre-diabetic patients when compared to that of clinically healthy individuals
Materials and methods: This is a descriptive cross-sectional study conducted in a tertiary care hospital in Tamil Nadu. The participants for this study were selected from the Non-Communicable Disease (NCD) Clinic of the hospital and from the community. The recording of event related cognitive evoked potential response for all the participants was recorded in the research lab - human experiments laboratory in the department of Physiology.
Results: The N1 latency (msec), P2 latency (msec), N2 latency (msec) and P300 latency (msec) in prediabetics were 132.6±34.4, 179.7±36.6, 246.6±39.9 and 346.2±27.6. The N1 latency (msec), P2 latency (msec), N2 latency (msec) and P300 latency (msec) in controls were 111.5±10.2, 153.6±9.5, 205±15.1 and 317±11.3. The N2-P300 amplitude (mvolt) in prediabetics and control were 3.6±1.6 and 6.1+4.2 respectively. The difference is statistically significant. ($p<0.05$)
Conclusion: There exists a prolonged latency and decrease in amplitude in pre-diabetic patients which was proved significant, compared to normal individuals.

Keywords: Prediabetes, Cognition, Cognitive evoked potential, Impaired glucose tolerance, Impaired fasting glucose.

INTRODUCTION

Diabetes mellitus is a major public health problem, the incidence of which is increasing worldwide. The prevalence of diabetes continues to increase by 49% in last decade.[1] Prediabetes (Impaired Fasting Glucose and Impaired Glucose Tolerance) leads to increased risk of cerebrovascular, cardiovascular changes and they are in more risk to develop diabetes in future.[2]

Young adults are more prone to develop prediabetes. The worldwide prevalence of Impaired Glucose tolerance(IGT) was found to be 343 million (7.8%).[1] This ranges from 5.8% in South East Asia to 11.4% in North American and Caribbean Countries. International Diabetes Federation says that the prevalence will increase to 471 million worldwide by 2035. In India the prevalence of Pre-diabetes is found to be 10.6%. It is found that 30 to 40% of subjects with IGT have the tendency to develop type 2 diabetes in future. Alberti says that the term 'Prediabetes' was first used to indicate abnormalities of pregnancy (e.g., high-birth weight babies, hydramnios) or family history of type 2 diabetes mellitus.[3] In 2005, American Diabetes Association (ADA) formed this term 'Prediabetes' to collectively indicate impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). In 2008, WHO suggested the term "intermediate hyperglycemia" to cover IGT and IFG.[4] But American Diabetes Association (ADA) is using the term 'Prediabetes' .[5]

Many studies have shown that there is increased risk of developing cognitive dysfunction in diabetic individuals.[6] Only few studies reveal that pre-diabetics are prone for cognitive dysfunction. [7]

According to American Diabetes Association (ADA), a person is said to be pre-diabetic if he/she fulfils any one of the following criteria

1. Fasting plasma glucose of 100 to 125mg/dl (Or)
2. Impaired Glucose Tolerance (IGT) of 140 to 200 mg/dl after ingestion of 75g of oral glucose load.

One of the earliest neurological complications of prediabetes was found to be cognitive dysfunctions. Though various reasons, Anna Marseglia et al says that the neurological complications in hyperglycemia may be due to the following reasons.

(i) Hyperglycemia in brain may lead to neuronal death. This may result in cognitive dysfunctions over time. [8]

(ii) Hyperglycemia may develop mutations in neuronal and glial cell functioning. This can lead to the production of reactive oxygen species, which results in oxidative stress, advanced glycosylation end-products (AGEs) formation, activation of advanced glycosylation end-products receptors. These changes will terminally lead to produce atherosclerosis in cerebral blood vessels.

(iii) In hyperglycemia brain atrophy and blood volume reduction is seen. This may lead to cognitive decline.[9]

So, the objective of this study is to assess the early onset cognitive dysfunction in pre-diabetics. If diabetes is causally related to cognitive impairment, one also might expect to observe impaired cognitive performance in those with impaired fasting glucose (IFG) levels or "prediabetes."

Therefore, we sought to determine the association between pre-diabetes and cognitive function and risk of developing cognitive impairment in pre-diabetic patients.

Cognitive dysfunction in patients with diabetes mellitus was first noted in 1922, when patients with diabetes, who were "free from acidosis but usually not sugar free," were noted to have impaired memory and attention on cognitive testing compared with controls. [10] Since then, there have been many studies designed to better delineate the scope and magnitude of cognitive dysfunction in diabetes.

There have been controversial reports regarding effect of diabetes on cognitive functions. Most of the psychometric studies' employing variety of tests, assessing psychomotor speed, selective attention, lexical fluency, auditory verbal learning, showed that scores were lower in diabetics as compared to controls.[10–12]

Cognition refers to all the mental activities involved in receiving information, comprehending it, sorting, retrieving, and using it. It is associated with goal directed behavior and helps the individual in adjusting with the changing environmental needs.[13] Tomas Paus says that anterior

cingulate gyrus and prefrontal cortex in brain are responsible for cognition.[14] Cognitive evoked potential is one of the various tests available to test cognition.

Long latency evoked potentials are related to cognitive processing and are referred to as cognitive evoked potential (CEP). P300 is the most frequently investigated Cognitive Evoked Potential appearing at about 300 millisecond following task-related stimuli. P300 can be elicited by any stimulus, the most common being an unexpected or infrequent stimulus (oddball paradigm). This involves presentation of unexpected, infrequent stimuli randomly interspersed among frequent stimuli. The character of unexpected stimuli differs from the common stimuli in terms of frequency or intensity. Two factors

(i) stimulus infrequency or unexpectedness and
(ii) attention to task relevance operate independently.

Unexpectedness of stimuli and attention to it produce different evoked potentials. These evoked potentials are called as cognitive evoked potential. The P300 component is considered for analyzing the subject's cognition. This test reflects the subject's cognitive skill level and verifies whether disorders are present in the auditory association cortex. So cognitive evoked potential is used to assess early cognitive dysfunction in pre-diabetic individuals.

AIM:

To evaluate whether cognition is impaired in the pre-diabetic patients when compared to that of clinically healthy individuals

OBJECTIVES:

To estimate the change in variables of cognitive evoked potential response in the prediabetic individuals and to compare the same with clinically normal healthy individuals of the study group.

MATERIALS & METHODS

This is a descriptive cross-sectional study conducted in a tertiary care hospital in Tamil Nadu. The participants for this study were selected from the Non-Communicable Disease (NCD) Clinic of the hospital and from the community.

The recording of event related cognitive evoked potential response for all the participants was recorded in the research lab - human experiments laboratory in the Department of Physiology.

This study was started after obtaining Institutional ethics clearance and written informed consent from all the participants. Statistically adjusted sample size of 100 participants was taken as study group and they were categorized into case study group (n=50) and control group (n= 50). In the case study group, patients were clinically diagnosed as pre-diabetic based on the OGTT. In which fifty pre-diabetic patients of both the gender were selected in the age group of 25-50 years from Non-Communicable Disease (NCD) clinic (cases). The control group was randomly selected from the community, in which fifty healthy individuals of both the gender in the age group of 25-50 years were involved in this study

Inclusion criteria:

Case study group

- Clinically diagnosed pre-diabetic patients based on OGTT
- Age group of 25-50 years of both the gender

Controls

- Clinically normal healthy individuals
- Age group of 25-50 years of both the gender

Exclusion criteria:

- People in age group of < 25 and >50 years of both the gender.
- Participants who are smokers and alcoholics
- Patients who were clinically diagnosed as type I DM and type II DM with/without treatment
- Patients who had hearing loss

- Patients who were clinically diagnosed of any endocrinological diseases such as Cushing's disease, acromegaly, pheochromocytoma, chronic pancreatitis, pancreatectomy, dumping syndrome, sub-optimally treated thyroid disease and currently pregnant
- Patients who are under treatment of drugs (that will alter glucose metabolism) such as glucocorticoids, pentamidine, nicotinic acid, diazoxide, beta-adrenergic agonists, thiazides, Dilantin, interferon alpha, retroviral drugs and anti-neoplastic drugs.
- Patients with any other chronic illness such as hypertension, tuberculosis, chronic kidney disease, coronary artery disease, etc.
- Patients with any other neurological, psychiatric disorders.

PROCEDURE

This study was started after giving clear instructions and demonstration of the procedure involved to all the participants of the study group. Any doubts of the participants were clarified. Adequate time and rest were ensured to all the participants.

After enrolling the participants in the study, a thorough clinical examination was done. It was followed by assessment of their socio-demographic details like socio-economic class, education status, height, weight, etc. A definite date and time were given to all the participants to visit the research lab, for recording the event related cognitive evoked potential.

Patients visiting the NCD were subjected to OGTT from which the initial 50 patients diagnosed of pre-diabetic were included in the case study group.

Assessment of Oral Glucose Tolerance Test (OGTT):

This test was done at the central clinical laboratory. The OGTT was administered following an overnight fast in the morning. After the initial venous blood sample, participants drank 75g anhydrous glucose over 5 minutes. A second blood sample was taken 2 hours later which was taken as the post load blood sugar level of the participant.

Electrophysiological evaluation:

Endogenous-event-related potentials were obtained, using the tonal P300 oddball paradigm, on all the participating subjects. The P300 wave is a late cortical neurophysiological event and is considered to reflect the speed of neuronal events underlying information processing. It appears to be strongly associated with attention and short-term memory, P300 was recorded in the study group at the research lab - human experiments lab. The procedure was explained in detail, demonstrated once and the doubts if any raised were clarified to all the participants. The recording of event related cognitive evoked potential (P300) was done in a daytime. The event related cognitive evoked potential (P300) was recorded using MEDICAID Neurostim machine by giving odd ball paradigm stimuli. The reliability of the values obtained was ensured by taking thrice the recording for each participant at three different time points and the average of those three recordings was considered.

The subjects were presented with two types of auditory stimuli, a target and non-target stimuli through head phones in both the ears. The target tone (infrequent stimuli-2 kHz) and the nontarget tone (frequent stimuli - 1 kHz) used were presented over headphones at an intensity of 70 dB. They were presented with a probability of 20% to the left and right ears separately. The auditory stimuli were presented at the rate of 1.25s which of pure tone type. Totally 50 target stimuli were given. The duration of each stimulus was 100 ms. The ratio of target and non-target stimuli was 4:1.

An initial trial was given to the patient for the easy identification of the target stimuli. The subject was asked to silently count all the target tones, ignoring the non-target tones, and to report the total at the end of the test (target test).

Statistical Analysis

All data were evaluated and analysed using Statistical Package for Social Sciences (SPSS) 26.0. The data obtained from our study results were categorical and continuous data. The categorical variables were represented in range, where the continuous variables were represented as mean±SD. The normality was assessed using Kolmogorov-Smirnov test. The samples were normally distributed. Student's 't' test was used to compare the continuous variables between the case study group and control group. P value < 0.05 was considered statistically significant.

RESULT

In our study we intended to compare the fasting and postprandial blood glucose levels, the latencies and amplitude of event related cognitive evoked potential between the pre-diabetic patients (n=50) and clinically normal healthy individuals (n=50).

(i) COMPARISON OF SOCIODEMOGRAPHIC DETAILS AMONGST THE STUDY GROUP:

Both the case study group and control group were age and sex matched. The mean of age, height, weight, BMI among the study group were depicted in table 1 as shown below.

Table 1: Comparison of age, sex, height, weight, BMI between the pre-diabetic patients and the control group.

Variables	Pre-diabetic patients (n=50)		Clinically normal healthy individuals (n=50)	
	Mean	SD	Mean	SD
Age (years)	36.1	5.9	35.7	6.2
Height (cms)	162.9	6.6	164.2	9.1
Weight (kgs)	67.9	7.9*	60.1	8.3*
BMI (kg/m2)	25.7	3.1*	22.4	1.4*

SD = standard deviation, BMI = Body mass index, * p<0.05 considered as statistically significant

(ii) COMPARISON OF BLOOD GLUCOSE LEVELS AMONGST THE STUDY GROUP:

The mean of fasting and postprandial blood glucose between the pre-diabetic patients and the control group were depicted in table 2 as shown below.

Table 2: Comparison of fasting and post prandial blood glucose levels between the pre-diabetic patients and the control group.

Variables	Pre-diabetic patients (n=50)		Clinically normal healthy individuals (n=50)	
	Mean	SD	Mean	SD
Fasting blood glucose (mg/dl)	114.0	7.5*	81.2	7.1*
Post prandial blood glucose (mg/dl)	166.1	14.8*	120.7	10.7*

SD = standard deviation, * p<0.05 considered as statistically significant

(iii) COMPARISON OF VARIABLES IN EVENT RELATED COGNITIVE EVOKED POTENTIAL (P300) AMONGST THE STUDY GROUP:

The mean of parameters of cognitive evoked potential (P300) – N1 latency (msec), N2 latency (msec), P2 latency (msec), P300 latency (msec) and N2 – P300 amplitude (mvolt) between the pre-diabetic patients and the control group were depicted in table 3 as shown below.

Table 3: Comparison of parameters of cognitive evoked potential (P300) – N1 latency (msec), N2 latency (msec), P2 latency (msec), P300 latency (msec) and N2 – P300 amplitude (mvolt) between the pre-diabetic patients and the control group.

Variables	Pre-diabetic patients (n=50)		Clinically normal healthy individuals (n=50)	
	Mean	SD	Mean	SD
N1 latency (msec)	132.6	34.4*	111.5	10.2*
P2 latency (msec)	179.7	36.6*	153.6	9.5*
N2 latency (msec)	246.6	39.9*	205	15.1*
P300 latency (msec)	346.2	27.6*	317	11.3*
N2 – P300 amplitude (mvolt)	3.6	1.6*	6.1	4.2*

SD = standard deviation, * p<0.05 considered as statistically significant

DISCUSSION

Our aim of the study was to find out if there is any change in the event related cognitive evoked potential in the pre-diabetic patients who were diagnosed following an OGTT in this study. However, to implement this, we had chosen 50 clinically normal health individuals as control group and 50 pre-diabetic patients as case study group.

When comparing the socio-demographic details among the study group, we found that the age and height were almost same in the control group as well as the case study group as depicted in the table 1.

In this study it was found that there was significant difference in the mean BMI between the normal subjects and the pre-diabetic patients. As per literature, this may be due to the presence of insulin resistance among the obese individuals. Steven M. Haffner et al have documented in his study that there was a significant difference in the BMI of the pre-diabetic persons and the normal individuals.[15]

Saczynski JS et al have also found that compared with normal healthy individuals, pre-diabetic patients had more mean BMI which is in favour of this study.[16]

Our study showed that, amongst the pre-diabetic patients, the P300 latency of event related cognitive evoked potential response (P300) was prolonged and also the amplitude was significantly reduced, when compared to that of the normal healthy control group. This implies the presence of a significant cognitive decline in the pre-diabetic patients as identified by the cognitive evoked response recording.

Satabdi Saha et al. did a cross sectional study on pre-diabetic patients and found out that P300 latency was significantly increased in pre-diabetic individuals compared with normal subjects [13]. This was very consistent as like our study results. It was proven by earlier studies that those individuals with impaired glucose tolerance and hyperinsulinemia were found to have decreased Mini Mental State Examination (MMSE) scores[7] and they were at increased risk for mild cognitive impairment(MCI). These results were supportive to our study.

In another study conducted by Yaffe K et al, on postmenopausal women, women in study group were classified into three groups – diabetes, prediabetes and normal glucose level. They found that women with prediabetes tended to have decreased cognitive scores and rates of cognitive decline were intermediate between those women with diabetes and those with normal plasma glucose level. [17]

Antonio Convit et al had reported an association between peripheral glucose regulation and the volume of the hippocampus, which was intended to evaluate the impact of changes in glucose levels in learning and memory. They found that individuals with poorer peripheral glucose regulation were more likely to have lower memory performance and smaller head size adjusted hippocampal volumes. But these fMRI changes were present only in hippocampus. [18]

Matti Vanhanen et al had conducted a study on Finnish elderly population. They encountered that subjects with impaired

glucose tolerance had lower mini mental state examination (MMSE) and Buschke Selective Reminding Test (BSRL) scores which was statistically significant when compared with subjects with normal glucose level.[19]

Results demonstrated that reduction of glucose level in diabetic subjects takes to increase in latency and reduction of amplitude of component P300, suggesting that there is central auditory system dysfunction. Considering that nervous tissue is glucose- dependent, that is, it depends on stable glucose levels in ideal situations, episodes of hypoglycemia for prolonged periods of time may take the subject to significant neurological deficits. Thus, the investigation of P300 cognitive potential may be an important procedure for prevention and early diagnosis of neurological affections in subjects with Diabetes Mellitus

In this study we had included prediabetes patients and made an attempt to demonstrate the presence of any cognitive decline using a non-invasive recording of cortical activity via an auditory stimulus in these pre-diabetic patients.

CONCLUSION

In our study, results strongly suggests that there exist a prolonged latency and decrease in amplitude in pre-diabetic patients which was proved significant, in spite of slight variations in BMI that was present between the case study and the control group.

Henceforth, the results obtained with the present study allowed us to primarily conclude that an investigation with P300 cognitive potential could be an important tool for early diagnosis of neurological deficits in patients diagnosed of pre-diabetics. Relying on our results we insist that the pre-diabetic patients should be screened in out-patient department on regular basis for cognitive decline to detect early cognitive impairment if any. This can lead to the possible interventions that could be made to prevent further cognitive decline.

Limitations:

- We did not assess cognitive function with a standard battery of cognitive tests that might assesses five different domains.
- It was a cross-sectional study
- The observer was not blinded in this study. So, this would have affected the study

Future Directions:

- The Pre-diabetic patients could be given treatment to keep the blood sugar level under control and the cognition can be assessed to know whether there is any improvement
- Other neurological tests could be used to assess cognition in specific domains

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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