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Neuropsycological Assessment in Patients with Prediabetes: A Case Control Study

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ABSTRACT:
Background and Aim: Pre-diabetes is a condition in which blood glucose level is higher than normal but not high enough to be diagnosed as diabetes. This elevated blood sugar level may have an impact on neuropsychological status of an individual with pre-diabetes. The aim of this study is to assess the neuropsychological parameters in patients with pre-diabetes.
Materials and method: Twenty five pre-diabetic patients attending the endocrinology outpatient department of MS Ramaiah Medical College and Hospital were recruited for the study. Twenty five age, sex and education matched normal subjects were enrolled for the study.
Detailed history was taken. A thorough general physical examination and systemic examination was done. The subjects were divided into the two groups based on their serum HbA1C level. Neuropsychological assessment was done using a validated questionnaire Adenbrooke's Cognitive Examination-III (ACE-III).
Result: ACE-III score was in normal range in prediabetics. A statistically significant reduction was found in ACE-III score between controls and patients with pre-diabetes.
Conclusion: A significant reduction in ACE-III score indicates the initiation of neuropsychological impairment in patients with prediabetics. Our study shows an early onset of cognitive decline in pre-diabetes compared to normal subjects.
Keywords: Pre-diabetes, Neuropsychological assessment, ACE-III
Abbreviations used: ACE-III: Adenbrooke's Cognitive Examination, AD: Alzheimer's disease, AGE: Advanced glycation end product, BMI: Body Mass Index

I. INTRODUCTION:

Pre-diabetes is an intermediate group of individual whose blood glucose level is higher than the normal, though not high enough to diagnose as Diabetes. Prediabetics have a higher chance of developing type 2 diabetes mellitus if their blood glucose level is not controlled at this stage. It is often associated with obesity, dyslipidemia and hypertension[1]. Pre-diabetes is also found to be associated with development of early atherosclerotic changes in the blood vessels[2]. Insulin resistance, hyperglycemia, accumulation of advanced glycosylation end products and formation of reactive oxygen species can be seen even in case of prediabetes[1]. These changes can lead to development of neurological complications. Neurological defects may occur in the form of slowness of intellectual functions, lethargy, memory deficits, depression, cognitive dysfunction etc. Very few studies have been done to assess the neuropsychological status in pre-diabetes.

Neuropsychological evaluation is done to assess the performance of brain. The abilities tested include language, attention, learning, processing speed, reasoning, memory, problem solving and more. Adenbrooke's Cognitive Examination III is a useful neuropsychological test for assessing cognitive profile of an individual.[3] It is a simple, brief, bedside test and takes only 10-15 minutes to perform. It does not require any specialized equipment. ACE-III also incorporates the cognitive domains assessed by Mini-Mental State Examination (MMSE). In this study we have assessed neuropsychological parameters using ACE-III score in prediabetics.

Methodology: Twenty five pre-diabetes patients attending the endocrinology outpatient department of MS Ramaiah Medical College and Hospital were recruited for the study after getting the informed consent. Twenty five age, sex and education matched healthy controls were enrolled for the study. The study was conducted from January 2015 to April 2016. The study subjects were divided into 2 groups. Control group (group1) included age, sex and education matched normal subjects. The cases (group2) comprised of both male and female patients with pre-diabetes in the age group of 20 - 50 years. Patients with past or present history of psychiatric and neurological disorder, history of eye disease, chronic alcoholics and chronic smokers, history of thyroid and renal disorder,

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patients on drugs which may alter the psychomotor function and patients with acute or chronic liver disease has been excluded from the study.

Ethical clearance was obtained from the authority. Testing procedures were explained and consent was obtained from the cases and controls. Detailed history was taken. A thorough general physical examination and systemic examination was done. The subjects were divided into the two groups based on their serum HbA1C level. Serum HbA1C level was estimated by High Performance Liquid Chromatography (HPLC). Neuropsychological assessment was done using a validated neuropsychological questionnaire ACE-III.

ACE-III was introduced and subjects were explained about the procedure of the questionnaire. Assessment of neuropsychological parameters in ACE-III is based on attention, memory, verbal fluency, language and visuospatial ability. Attention was assessed by asking the subject about date, time and place and to repeat some words that have been given to them. For assessing attention they were also asked to perform some simple calculations. Memory was assessed by asking the subject to remember few words and one address. Fluency was examined by asking the subject to name as many animals as possible in one minute. For assessing language, subjects were asked to follow some verbal commands and to write few sentences about their last holiday/weekend/festival. They were also asked to repeat some words & sentences and name few pictures shown to them to assess language. For assessment of visuospatial abilities, subjects were asked to copy some diagrams, to draw a clock, to count dots without pointing them and to identify few letters. This test took 10-15 minutes to perform. Based on their answers to the questionnaire, scores have been given to assess the cognition.

II. STATISTICAL ANALYSIS

The parameters were tested for normal distribution. Parametric data were described in terms of mean and standard deviation (mean ± S.D.). ANOVA was used to analyze the differences in mean between the groups. Two-way ANOVA was used to adjust for the age. Post hoc comparison between the groups was done using Bonferroni test. P-values less than 0.05 were considered significant. Statistical analyses were done using SPSS version 17.0.

III. RESULTS:

The study was conducted on 25 normal subjects and 25 pre-diabetes patients. The participants were between the age group of 20-50 years. The mean age of normal subjects and prediabetics were 25.88 ± 5.76 and 31 ± 3.89 years respectively. In controls, 15(60%) were female and 10(40%) were male. In cases, 13(52%) females, 12(48%) males were there. The gender distribution in the study groups was comparable (P = 0.687).The mean HbA1C levels in control group and cases were 5.14 ± 0.21 and 6.02 ± 0.21 % respectively. The basic parameters are described in **Table 1.**

Table 1: basic parameters in study groups

PARAMETERS	**CONTROLS MEAN ± S.D.**	**CASES MEAN ± S.D.**	**P-VALUE**
AGE	25.88 ± 5.76	31.12 ± 3.89	> 0.05
SEX (M/F)	10/15	12/13	0.687
HbA1C%	5.14 ± 0.21	6.02 ± 0.21	< 0.001

ACE-III scores in control group and prediabetics were within normal limit (>88). However, when the scores between the three groups were compared, the difference was found to be statistically significant. The mean ACE-III score in control group and pre-diabetic group was 96.88 ± 1.36 and 94.08 ± 2.51 respectively as shown in **Table 2.**

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Table 2: Comparison of ACE-III scores between controls and cases

Study group	Mean ACE-III	S.D.	P-value
Controls	96.88	1.36	<0.001*
Cases	94.08	2.51	
*Significant- P-value: P<0.05			

IV. DISCUSSION:

Pre-diabetes is an increasing global health problem of the 21st century. Each year more and more people live with this conditions which can lead to life-changing complications. In many studies type 2 DM in elderly has been found to be associated with cognitive impairment[4,5,6,7]. Very little is known about the neuropsychological status of people with pre-diabetes because of limited number of studies available in the literature. It is important to know the neuropsychological status in prediabetics to avoid further deterioration of cognition to maintain better quality of life. In the present study neuropsychological parameters were compared between prediabetics and normal subjects by a validated neuropsychological test ACE-III. ACE-III scores in all the study groups were found to be within normal limit (> 88). However, when the ACE-III scores were compared between control group and pre-diabetic group the difference was statistically significant (P=0.000). Pre-diabetic group had lower ACE-III scores as compared to healthy subjects. Lower ACE-III scores in prediabetics may indicate the initiation of cognitive decline in these groups of individuals even before developing type 2 DM.

In the study conducted by Jose A. Luchsinger et al, executive function was found to be worsened in pre-diabetic stage[8]. Weili Xu et al concluded in their study that diabetes and - accelerate the progression from mild cognitive impairment to dementia[9]. Result of the study conducted by Nazaribadie M et al showed significant differences in cognitive function in patients with type 2 DM and pre-diabetes when compared with normal subjects[10]. These results support the findings of the present study. Prolonged hyperglycemia leads to formation of advanced glycation end product (AGEs) which have a deleterious effect on neurons, glial cells and myelin sheath[11,12]. AGE mediated brain injury may be a cause of cognitive decline in pre-diabetes and type 2 DM. Increased blood glucose level causes to activation of Protein kinase C. Activated PKC can lead to atherosclerotic changes in the blood vessels which can retard the blood flow to the brain[4] that can also contribute to the neuronal degeneration. Hyperglycaemia is also proposed to cause tissue damage by increasing the generation of reactive oxygen species[26]. Combined effect of all these factors has been postulated to cause neuronal damage in the brain. In the presence of neuronal damage, processing of information may be delayed, leading to impaired cognitive function. Self-care ability of prediabetics will be affected due to cognitive impairment which can also accelerate the development of diabetes. All pre-diabetic patients should be screened for neuropsychological impairment at the time of diagnosis and regularly thereafter to improve the quality of life.

V. CONCLUSION:

Pre-diabetes was found to be associated with reduced ACE-III scores compared to the normal subjects. These findings suggests the existence of cognitive decline even in pre-diabetes stage itself before the development of type 2 DM.

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