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Evaluation Of Cognitive Evoked Potential P_{300} And Its Correlation To Serum Insulin Levels In Alcohol Dependence Patients.

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ABSTRACT

Alcohol dependence, points to the evidence of impairments from alcohol in multiple areas of life functioning, despite which the person returns to drinking. A central descriptive characteristic of the dependence syndrome is the strong overpowering desire to take alcohol and evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals. To correlate P_{300} values with serum Insulin level in alcohol dependence individuals and to evaluate whether insulin can be kept as a biomarker for cognitive functioning .The study was conducted in the Institute Of Physiology and Experimental Medicine of Madras Medical College and psychiatry department of the Rajiv Gandhi Government General Hospital, between September 2016 and February 2017 after obtaining approval from the Institutional Ethics Committee (IEC) at the Madras Medical College, Chennai-3.The mean P_{300} amplitude in the case group is 6.31 ± 1.8 and in the control group is 9.5 ± 1.4. It is clearly seen that there is extreme statistical significance between the case and the control group as the p- value is 0.0001. The mean serum insulin value of the case group is 13.26 ± 12.81 and in the control group is 6.18 ± 3.34. It can be seen that the comparison is very statistically significant as the p-value is 0.0049. The mean of the fasting blood sugar value of the case group is 93.7± 12.1 and the control group is 68.13 ± 8.41. The p-value is 0.0001. The correlation between serum insulin level and P_{300} latency of the case group shows a strong uphill linear relationship as the R value is > 0.70. The correlation is extremely statistically significant because the p value for the R is 0.00001. There, is significant correlation between the P300 latency and the serum insulin level and also the P300 amplitude and the serum insulin level in the alcohol dependence patients, hence serum insulin can be used as a cognitive marker in alcohol dependence patients.

Keywords: Event-related potential P300, type 2 diabetes mellitus, cognitive function, serum Insulin

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INTRODUCTION

Excessive alcohol consumption has become a major health concern in most countries inworld today. According to World Health Organisation (WHO) the global prevalence of alcohol dependence among adults worldwide ranges from 0% to 16% in 2004 [1, 2].

The prevalence among men were more than among women. The prevalence rate in Eastern European countries were high for both men and women. The prevalence rate in men suggests that numerous determinants such as environmental, individual, and genetic factors could favour evolution toward alcohol-dependence. Among environmental factors, quality of the neighbourhood or socio-economic factors (e.g., lower educational level, employment status) may increase risks of alcohol abuse. Individual and psychological characteristics including comorbid psychiatric disorders, early life stress exposure, impulsivity are also risk-factors associated with chronic alcohol consumption. In addition, family studies, twin studies and adoption studies have highlighted that genetic factors play an important role in the pathogenesis of alcohol-dependence. Heritability of alcohol-dependence is estimated between 50and 80%and is considered as a complex polygenic phenotype. The average alcohol dependent person's life span decreases by 10-15 years [3, 4]. Cognitive dysfunction in alcohol dependence patients is gaining more importance as many studies are confirming that 50% to 80% of these patients present with cognitive impairment without any other neurological abnormality. These impairments are usually moderate to severe and donot come to notice unless specifically investigated for. These cognitive dysfunctions have been found to persist even after abstinence [5, 6].

Neuropsychological studies shows progressive disturbances in the cognitive functions like memory and frontal functions in alcohol dependence. Alcohol dependence affects working memory, executive functions, planning and solving complex problems or undertaking decisions. Alcohol dependence constrain the possibilities of flexible changes of action strategies, reduce behaviour control and suppress psychosocial adaptation abilities. The typical neurocognitive profile found in chronic detoxified alcoholics after 2 to 4 weeks abstinence is intact IQ and verbal skills, but impairment of novel problem solving, abstract reasoning, learning and memory, visuospatial analysis and complex perceptual-motor integration [7, 8]. Cognitive evoked potential or event related potential P_{300} isa cognitive neuroelectric phenomenon because it occurs when subjects attend to psychological tasks and discriminate stimuli that are different from each other. This discrimination produces a large positive wave form with modal latency of 300 ms and an amplitude of about 10 to 20 μV [9]. Explanation forP_{300}wave generation was first given 52 years ago as the basic information processing mechanism of attention al location and immediate memory by Sutton, braren, Zubin and John. Interest in P_{300} as a means to assess cognitive function increased dramatically [10]. The hypothesis of this study is that the latency of the cognitive related potentialP_{300}inalcoholdependenceindividualswillbeprolongedcomparedto the non-dependent individuals [11]. The Insulin levels in alcohol dependent individuals will be higher than the non-alcohol dependent individuals and that there will be a positive correlation between theP_{300} latency and insulin levels [12].

MATERIALS AND METHODS

The study was conducted in the Institute Of Physiology and Experimental Medicine of Madras Medical College and psychiatry department of the Rajiv Gandhi Government General Hospital, between September 2016 and February2017after obtaining approval from the Institutional Ethics Committee (IEC)at the Madras Medical College, Chennai-3. Total of 66 males in the age group of 18-50 years were screened for participation in the study. Thirty healthy men in the age group of 18-50years, who are nondiabetic and do not consume alcohol were taken as control group. Out of thirty-six male patients screened for participating in the study six of them were rejected as two of them had type 2 Diabetes mellitus and the other four patients had chronic pancreatitis, cirrhosis of liver, history of head injury and history of bipolar disorder. So, thirty men who are in the age group of 18-50 years, non- diabetic and satisfy the alcohol dependence criteria ofICD10 is selected as case group. In total sixty men in the age group of18-50 years were selected for the study.

Inclusion Criteria

- Thirty patients – non diabetic men who satisfied the criteria for alcohol dependence according to ICD 10 in the age group of18-50 years will only be taken as case group.

- Thirty non-alcohols consuming and non-diabetic men in the age group 18-50 years were taken as controls from general population
- Educated for a minimum of five years.
- Normal hearing ensured by history and testing.
- Alcohol dependent patients who are abstinent at least for a week are only taken in the case group.
- Subjects who gave informed consent were only included in the study.

Exclusion Criteria

- Type I Diabetes mellitus, Type II Diabetic mellitus, subjects were screened by taking fasting and post prandial blood sugar, those with blood sugar in the diabetic range were excluded from the study.
- Mental retardation
- History of any other Psychiatric illness
- Neurological or medical illness that could affect cognitive functioning.
- H/O head injury with loss of consciousness
- H/O other substance dependence
- H/O intake of Benzodiazepine or other drugs that could impair cognition.

Sixty men of age group between 18-50yrs were included in the study. Thirty non diabetic alcohol dependence patients from the Psychiatry OP of the Rajiv Gandhi Government General Hospital were selected based on the inclusion and exclusion criteria and were taken as case group. Thirty healthy non alcohol consuming, non-diabetic people satisfying the inclusion and exclusion criteria were taken as the control group.

Electrophysiological Assesment P_{300} Event Related Potential

The participants in the study were informed to have a hair wash on the day of doing the event related potential P_{300}. After explaining the procedure of the P300 in detail, clarifying the doubts and obtaining informed consent, P_{300} auditory event related potential was measured in the patient and control group at the research lab in Rajiv Gandhi Government General Hospital. An initial trial was given for the patient so that they can identify the target stimuli easily. The event related potential is recorded using the MEDICAID Physio-pac 2 channel neurostim machine. The event related potential P_{300} is recorded while performing an odd ball paradigm. It was explained to the subjects that they will be presented with two types of auditory stimuli in the testing, a nontarget stimuli and a target stimulus through head phones in both of their ears. The auditory stimuli were of pure tone type presented at the rate off or 1.25 s, a total of 100-150 stimuli are given. Each stimulus durationwas100msandwithanintensity of70 db. The nontarget stimuli and the target stimuli presented in the ratio of 80% and 20%. The stimuli that the participants did not respond to will be rejected and the rest of the waves for the target stimuli will be taken up for calculating the P_{300}. Initial demonstration is given before the test is done. P_{300} is assessed interms of its latency and amplitude. Latency is taken as the time from the stimulus application to the onsetofresponseitisusuallybetween250-400milliseconds.Amplitudeisthemeasure between the pre stimulus baseline and the largest positive peak in event related potential in the latency window of 250–400 milliseconds. The amplitude is usually of 10 μV value in normal individuals. It is the P3b component of the P3 wave that is considered extensively for measuring cognitive evoked potential, so this was measured at Pz. The reference, ground and active electrodes were placed according to the 10-20 international system of electrode placement.

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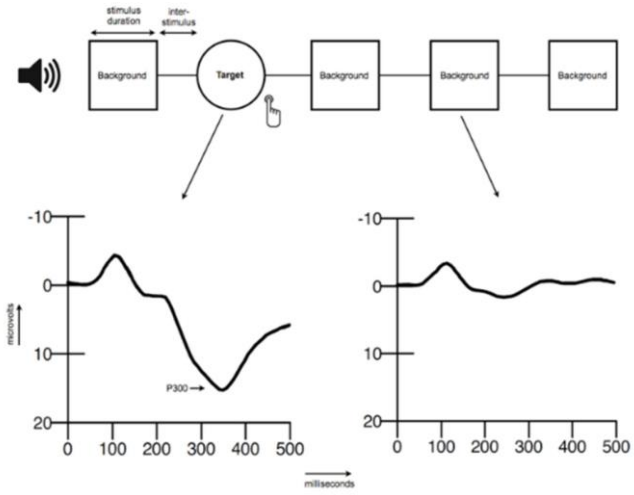

Figure 1: P_{300} wave Generation By Target Stimuli and Waves Generated By Background Stimuli

Estimation Of Fasting Blood Sugar Levels

The patients were asked to come in fasting state for blood sample collection. The antecubital vein is chosen for withdrawing blood. About 3ml of blood was withdrawn using a hypodermic needle and the blood was transferred in to a clot activator tube. The sample is then taken to the biochemistry department. Then the sample is centrifuged at 3000 rotations per minute for ten minutes. The superficial serum is then collected by a micropipette and transferred in to an Eppendorf tube. This Eppendorf tube is closed tightly and is stored in the Deepfreezerat-20degreeCelsiusat the research lab of Institute of Physiology and Experimental Medicine at Rajiv Gandhi Government General Hospital. All the samples were collected in this method. Estimation of serum fasting blood glucose levels was done by Electrochemiluminescence immunoassay method using Roche Diagnostics Cobas GLU HK Gen .3 kit that contains invitro diagnostic reagent system. The test was done at the central lab of the Institute of Biochemistry at Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

Estimation Of The Fasting Serum Insulin Levels: Sample Collection And Storage:

The patients were asked to come in a fasting state for the sample collection. Under strict aseptic precautions about 3ml of blood sample was withdrawn from the antecubital vein into a clot activator tube. This sample was taken to the biochemistry department the blood was centrifuged and superficial serum collected from the subject and was centrifuged at 3000 rotations for 10 minutes, then the separated serum is taken by a micropipette and stored in an Eppendorf tube. The Eppendorf tube was stored in a deep freezer at -20 degree Celsius. After collection of all the samples, estimation of serum fasting insulin levels was done by Electrochemiluminescence method using the Roche Diagnostic Insulin kit. The test was done at the central laboratory of the Institute of Biochemistry at the Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

Statistical Analysis Plan

The data analysis was done using SPSS VERSION 21 software. The analysis includes both the comparison of the values of the same variable between the case and the control group and the correlation between the variables within the group. The following statistical plans were used. For comparing the age, event related potential P_{300} latency, amplitude, the serum insulin level and fasting blood sugar values between the case and the control group the unpaired student "t" test was used. For correlation between the variables within group Pearsons's correlation was used.

RESULTS

This is a cross-sectional study conducted on two groups. One group is a study group containing alcohol dependence patients, the other group is a healthy volunteer group. Total of 60 participants were

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there of which 30 person were in the study group and the other 30 person were in the control group. The results of the cases and control group are discussed here.

Table 1: Basic Parameters Of The Case And The Control Group

S.NO	VARIABLE	MEAN±SD	
		CASE GROUP	CONTROL GROUP
1	AGE (in years)	38.1±7.15	39.2±6.82
2	P_{300}LATENCY (in ms)	358.78± 8.89	340.19± 4.53
3	P_{300}AMPLITUDE (in μv)	6.31±1.8	9.5±1.4
4	FASTINGSERUMINSULIN LEVELS (in μu/ml)	13.26±12.81	6.18±3.34
5	FASTINGBLOODSUGAR LEVELS (in mg/dl)	93.7±12.1	68.13± 8.41

The baseline parameters discussed in the study are given with the mean and standard deviation in Table 1.

TABLE 2: COMPARISONBETWEENTHEAGEOFCASEANDCONTROLGROUP

	GROUP	N	MEAN	STANDARD DEVIATION	p-VALUE
AGEIN YEARS	CASES	30	38.1	7.15	0.544
	CONTROL	30	39.2	6.82	
p<0.05isonlysignificant.					

The comparison of the mean of the ages between the case and the control group is given in table-2. The mean age of the case group is 38.1±7.15 and the control group is 39.2 ± 6.82. We can see that there is no statistical difference between the ages of the case and control groups as the p-value is more than 0.05.

Table 3: Comparison Of P_{300} Latency Between The Case And The Control Group

	GROUP	N	MEAN	STANDARD DEVIATION	p-VALUE
P_{300}LATENCY IN MILLISECONDS	CASES	30	358.78	8.89	0.0001**
	CONTROL	30	340.19	4.53	
**p-value:0.0001-Extremelystatistically significant.					

The comparison between the means of the P_{300} latency between the case and control group is given in table- 3. The mean latency of the case group was 358.78 ± 8.89 and the control group was 340.19 ± 4.53. There is extremestatisticalsignificancebetweenthecaseandthecontrolgroupP_{300} latency as the p-value is 0.0001.

Table 4: Comparison Between The P_{300} Amplitude In The Cases And Controls

	GROUP	N	MEAN	STANDARD DEVIATION	p-VALUE
P_{300} AMPLITUDE IN MICROVOLTS	CASES	30	6.31	1.8	0.0001**
	CONTROL	30	9.5	1.4	
**p-value: Extremely statistically significant.					

The comparison of the mean P_{300} amplitude between the case and control groups is given in the table-4. The mean P_{300} amplitude in the case group is 6.31± 1.8 and in the control group is 9.5± 1.4. It is clearly seen that there is extreme statistical significance between the case and the control group as the p-value is 0.0001.

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Table 5: Comparison Between The Serum Insulin Values Of The Case And The Control Group

SERUM INSULIN INμu/ml	GROUP	N	MEAN	STANDARD DEVIATION	p-VALUE
	CASES	30	13.26	12.81	0.0049**
	CONTROL	30	6.18	3.34	
**p-value: Extremely statistically significant.					

The comparison between the means of serum insulin in the case and the control groups is given in the table- 5. The mean serum insulin value of the case group is 13.26 ± 12.81 and in the control group is 6.18 ± 3.34.It can be seen that the comparison is very statistically significant as the p-value is 0.0049.

Table 6: Comparison Between The Blood Sugar Values In The Case And The Control Group

BLOOD SUGARIN mg/dl	**GROUP**	**N**	**MEAN**	**STANDARD DEVIATION**	**p-VALUE**
	CASES	30	93.7	12.1	0.0001**
	CONTROL	30	68.13	8.41	
**p-value: Extremely statistically significant.					

The means of the case and the control groups are compared in the table- 6 Themeanofthefastingbloodsugarvalueofthecasegroupis93.7± 12.1and the control group is 68.13± 8.41. The p-value is 0.0001, this shows thatthereisextremestatisticaldifferenceoncomparisonbetweenthefasting blood sugar levels of the cases and control group.

Table 7: Correlation Between The P_{300} Latency And The Serum Insulin Levels In The Case Group

VARIABLE	CORRELATION	P_{300}LATENCY
SERUMINSULIN LEVEL	PEARSONS CORRELATION	0.794
	Pvalue	0.00001
p-value: Extremely statistically significant.		

The correlation between serum insulin and P_{300}latencyin the case group is given in table - 7 and The correlation between serum insulin level and P_{300} latency of the case group shows a strong uphill near relationship as the R value is > 0.70. The correlation is extremely statistically significant because the p value for the R is 0.00001.

Table 8: Correlation Between The P_{300} Amplitude and The Serum Insulin Levels In The Case Group

VARIABLE	**CORRELATION**	**P_{300}AMPLITUDE**
SERUMINSULINLEVEL	PEARSONS CORRELATION	-0.819
	p-value	0.00001
p-value: Extremely statistically significant.		

The correlation between the serum insulin and P_{300}amplitude in the case group is given in table-8. The correlation between the serum insulin level and P_{300} amplitude of the case group shows a strongdown hill negative correlation as the R value is -0.70.The correlation between the two variables is extremely statistically significant because the p value for the R is 0.00001.

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Table 9: Correlation Between The P_{300} Latency And The Serum Insulin Levels In The Control Group

VARIABLE	CORRELATION	P_{300} LATENCY
SERUMINSULIN LEVEL	PEARSONSCORRELATION	0.572
	P value	0.0009
p-value: Extremely statistically significant.		

ThecorrelationbetweentheP$_{300}$ latency and serum insulin in control group is given in table 9. The correlation between P_{300} latency and the serum insulin level in control group shows a moderate uphill positive correlation as the R value is 0.50. The correlation between the two variables is highly statistically significant as the P value is 0.0009.

Table 10: Correlation Between The P_{300} Amplitude and The Serum Insulin Levels In The Control Group

VARIABLE	CORRELATION	P_{300} AMPLITUDE
SERUMINSULINLEVEL	PEARSONS CORRELATION	-0.389
	p-value	0.034
p-value<0.05STATISTICALLYSIGNIFICANT		

The correlation between P_{300}amplitude and serum insulin level is given in table- 10. The correlation between the variables P_{300} amplitude and serum insulin level shows a moderate down hill linear relationship as the R value is -0.389. The correlation betweenthe twovariables is statistically significant as the p-value is < 0.05.

DISCUSSION

Cognitive dysfunction reduces the ability of the subjects to process and implement complex thinking and decisions. Insulin signaling in brain feeding behavior, gluco-regulation, , body weight, neuronal development, , and cognitive processes such as with executive functioning, learning, memory and executive functioning [11, 12]. Cognitive dysfunction is an important co morbidity that needs to be addressed in alcohol dependence. This aroused the need for screening subtle cognitive dysfunction in alcohol dependence which are often unrecognizable. Recognizing these asymptomatic cerebral changes and modifiable risk factors that influence cognitive changes in alcohol dependence to put forward preventive measures for this condition. The mean age of the case and the control group were 38.1 ± 7.15and 39.2 ± 6.82. The p value on comparing the means of the two groups was 0.544, as the p value is >0.05 this clearly shows that there is no significant difference between the age groups of the cases and the controls. The event related potential P_{300} was measured in both the cases and the control groups. The mean of the P_{300} latency for the case group was 358.78±8.89 whereas the mean latency for the control group was 340.19 ± 4.53. By unpaired 't' test the calculated p value was 0.0001 which shows that there was extreme statistical significance between the case and the control group. The P_{300} latency in the case group (alcohol dependence) was prolonged than that of the control group (non-alcohol dependent) [13, 14]. The P_{300} latency is a measure of the classification (of stimulus) speed that is the time taken to detect and process a stimulus. The shorter the latency the superior the cognitive performance. So, the latency prolonged in the case group shows that the cognitive performance is affected in the alcohol dependence patients. The mean of the P_{300} amplitude in the case and the control groups were 6.31 ± 1.8 and the 9.5± 1.4 respectively. The p value calculated to find the statistical significance between the groups turned out as 0.0001. This p value denotes that there is extreme statistical significance between the amplitudes of the study and the control group. TheP$_{300}$ amplitude is larger in the control group than in the case group. P_{300} amplitude reflects the neural activity related to memory that is when a new stimulus is compared with the existing memory. The amplitude reflects the strength of the memory formed during the encoding and the storage process that varies with the serial position sequence in recognition tasks. So, the larger the amplitude the better the cognitive performance [15-16]. The finding in this study is that the amplitude in the case group is less than that of the control group. This goes to show that the cognitive performance of the case group (alcohol dependence group) is inferior to the cognitive performance of the control group that is there is cognitive dysfunction in the alcohol dependence people. The mean serum insulin values of the case and the control group are13.26± 12.81and6.18± 3.34 respectively. The p value calculated by unpaired 't' test is 0.0049. As P value is less than 0.05, this denotes that there is a statistically significant difference between the insulin values of the study and the control group.

Hyperinsulinemia in non-diabetic patients by itself causes cognitive decline by causing micro and macrovascular damage. Chronic elevated insulin level causes secretion of cortisol. Hypercortisolemia results in decreased volume of hippocampus and decreased regional cerebral glucose metabolism. Hyperinsulinemia as such also contributes to elevated levels of inflammatory mediators like Interleukin-6 (IL-6) and C-Reactive Protein (CRP). This inflammatory mediator might cause neuronal pathology. It can be said from this that hyperinsulinemia in alcohol dependence is a cause for cognitive decline [17]. The mean fasting blood sugar values of the case and the control group are 93.7 ± 12.1 and 68.13 ± 8.41 respectively. The mean fasting blood sugar value of the case (alcohol dependence) group is higher than that of the control group. The p value calculated for the fasting blood sugar values by unpaired 't' test is 0.0001, so the difference in the fasting blood sugar values between the two group is extremely statistically significant. The alcohol dependence people without diabetes tend to have higher blood sugar values than non-alcohol dependent people. This high blood sugar level predisposes the alcohol dependence people to diabetes. The correlation between the P_{300}latency and serum insulin of the case group was done to determine if there was a correlation between the two variables. The correlation was done using the Pearson's correlation test. The r - value was calculated and it was found to be 0.794 . This suggests a strong positive linear relationship between the two variables. The P value calculated for the r-value is 0.00001 [18]. From the positive correlation obtained it can be understood that whenever the P_{300} latency increases the serum insulin value also increases. The p value obtained shows that there will be hyperinsulinemia in alcohol dependence patients whenever there is a prolonged P_{300} latency. P_{300} estimates the speed of processing a stimulus and is an established cognitive marker for alcohol dependence patients as confirmed by the studies of Kim et al and Arriero et al. As thereisastrongcorrelationbetweenP_{300}latency and serum insulin level in alcohol dependence patients, it can be derived that serum insulin can be taken as a cognitive marker in alcohol dependence patients. The P_{300} amplitude and serum insulin level in the case groups were correlated to find if there is a relationship between the two variables. The correlation was done by Pearson'scorrelation.Ther-valueobtainedwas-0.819, revealing that there is a strong negative linear relationship between the P_{300} amplitude and serum insulin levels in the case group. The P value calculated between the two variables is 0.00001. The negative r- value means that the two variables move in the opposite direction. That is whenever the P_{300} amplitude decreases the serum insulin level increases [19]. The P_{300} amplitude is a measure of the strength of the memory formed during encoding and storage that varies with the serial position sequence in recognition tasks. The P_{300}amplitudeis a measure of the cognitive performance. So, the larger the amplitude the better the cognitive performance. The P_{300} amplitude in the case group is less as there is cognitive effect in alcohol dependence people. As the P_{300}amplitude and serum insulin has a strong negative correlation it can be safely said that serum insulin level can be used as a marker for cognition in the alcohol dependence group. The correlation between the P_{300}latency and the serum insulin level was done to find if at all there is a relationship between the two variables in the general population. The correlation was done using Pearson's correlation [20]. The r- value calculated is 0.572 and the p- value is 0.0009. The r-value shows that there is a strong positive linear relationship between the two variables. As there isa positive correlation both the variables move in the same direction. From this we canderivethatthereisarelationshipbetweenthetwovariablesinthenormalpeople. The relationship is significant as the p- value is < 0.05 [21]. The decreasedP300 latency found in non-alcohol dependent people is associated with decreased insulin level and no tin the hyper insulinemic levels. There is a significant correlation between latency and serum insulin in the control group. In the alcohol dependence group also there is a significant positive correlation, this goes to show that abnormal high levels of insulin is associated with increased P_{300} latency and cognitive impairment. Hence, abnormal high insulin levels can be used as a cognitive marker in alcohol dependence [22]. Even though there isa correlation between serum insulin and P_{300} amplitude in the general population, the correlation between serum insulin and P_{300} amplitude in alcohol dependence group was significant and hence insulin can be used as a marker for cognition in alcohol dependence. Insulin resistance with resultant hyperinsulinemia and hyperglycemia is found in alcohol dependence patients and hence this might be the contributor for the cognitive impairment in the alcohol dependence people. The increased insulin level and blood glucose level found among alcohol dependence patients in this study might be due to insulin resistance [23].

CONCLUSION

The patients with alcohol dependence had significant impairment in event related potential P_{300} latency and amplitude when compared with controls. The alcohol dependence patients had significant increase in serum insulin level than the control group. The fasting blood sugar values are significantly higher in the alcohol dependence group when compared with the control group. There is

significant correlation between the P_{300} latency and the serum insulin level and also the P_{300} amplitude and the serum insulin level in the alcohol dependence patients , hence serum insulin can be used as a cognitive marker in alcohol dependence patients.

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