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ORIGINAL ARTICLE

SERUM CARBOHYDRATE DEFICIENT TRANSFERRIN: A SENSITIVE MARKER IN DIAGNOSING ALCOHOL ABUSE

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ABSTRACT

Introduction: *Alcohol is a psychoactive substance with dependence producing properties and the burden of disease and death related to alcohol consumption remains significant in most countries. Early detection and proper medication with counselling can restore the alcoholics to normalcy. There is a need for a specific assay procedure to detect alcoholics early, so that proper therapy can be instituted. The traditional biomarkers in liver function test (LFT) are more frequently used for diagnosing alcohol abuse but they have variable and limited sensitivity and specificity. Carbohydrate Deficient Transferrin (CDT) can be considered as a more sensitive and specific marker for diagnosing alcohol abuse. The aim of this study is to determine % CDT in alcoholics and compare it with other alcohol markers in respect with sensitivity and specificity. The results of the study will be helpful in assessment of the alcohol dependence patients and therefore in their early detection and management.*

Materials and Methods: *This is a hospital based comparative cross-sectional study carried out in Dharan. A total of 40 cases of alcohol abuse with ≥2 score in CAGE questionnaire and matched 40 subjects with no history of alcohol intake were enrolled in the study. Informed written consent and ethical approval were taken.*

Result: *Serum %CDT has the highest diagnostic efficacy followed by serum gamma glutamyl transferase (GGT), Aspartate Transaminase (AST), Alanine Transaminase (ALT), AST/AL, and ALP as a biomarker for diagnosing alcohol abuse. Serum %CDT has the highest sensitivity with 97.5% and specificity of 73% at a cut off value of 3.5% compared to serum GGT with the sensitivity and specificity of 87% and 73%, respectively at a cut off value of 33.5 U/L.*

Conclusion: *Serum %CDT is a better marker both in terms of sensitivity and specificity compared to other conventional markers and thus can be used as a tool to early diagnose the alcoholic cases and monitor the therapy and for early identification of the relapses in alcoholics during treatment.*

Keywords: *Alcohol Dependence, CAGE Score, Carbohydrate Deficient Transferrin, Gamma Glutamyl Transferase.*

INTRODUCTION

Alcohol is a psychoactive substance with dependence producing properties that has been widely used in many cultures for centuries. The alcohol consumption and problem related to alcohol use vary widely around the world, and thus the burden of disease and death remains significant in most countries.[1] The harmful use of alcohol ranks among the top five risk factors for disease, disability and death throughout the world.[2] The burden

of deaths related to alcohol consumption is greater than the proportion of deaths from HIV/AIDS (2.8%), violence (0.9%) or tuberculosis (1.7%). Also 5.1% of the global burden of disease and injury is attributable to alcohol, as measured in disability-adjusted life years (DALYS).[3] Our Nepalese society and alcohol consumption behaviour has a long-connected history.[4] It has deep rooted religious, cultural and traditional dimensions as well as social implications.[5]

Dependence predicts a course of recurrent problems with the use of alcohol and the consequent shortening of the life span by a decade. The WHO estimates that more than 200 million people throughout the world suffer from alcohol dependence.[6] Physicians are likely to identify only 20-50% patient with alcohol use disorders who are attending medical care.[7] The biochemical, clinical and social effects of alcohol abuse highlight the urgent need for objective and specific marker for alcohol related disease and for early detection of potential alcohol abusers. The CAGE questionnaire, among other methods, has been extensively validated for use in identifying alcoholism.[8] Early detection and proper medication with counselling can restore the alcoholics to normalcy but most of the time alcoholics ingeniously hide their disease state and present to the physician very late.[9] Moreover, the questionnaires that are routinely used to diagnose alcohol abuse may be subjected to untruthful responses.[10] So, there is a need for a specific assay procedure to detect alcoholics early, so that proper therapy can be instituted.

The traditional biomarkers such as Alanine Transaminase (ALT), Aspartate Transaminase (AST), Gamma Glutamyl transferase (GGT), Alkaline Phosphatase (ALP), Mean Corpuscular Volume (MCV) are more frequently used for diagnosing alcohol abuse but they have variable and limited sensitivity and specificity.[11] Carbohydrate Deficient Transferrin (CDT) can be considered as a more sensitive and specific marker for diagnosing alcohol abuse. %CDT has been found to be specific and sensitive for alcohol abuse.[12] American Psychiatric Association,2000 has also stated on its higher specificity than other biomarkers for alcohol abuse.

Since its discovery in 1976 AD[13], CDT has quickly become the focus of basic research and clinical studies. Currently CDT is recognized as an independent alcohol marker, with reliable sensitivity and specificity to identify heavy drinking.[14] Approximately, 200-300 reports on CDT and alcohol[15] have been published, but probably CDT levels determination is yet to be done in our Nepalese population. The study aims to see the changes in biochemical parameter and to evaluate the diagnostic efficacy of different tests in alcohol abuse in comparison to control. Considering the different alcohol taking customs associated with various tradition in eastern Nepal, evaluation of %CDT determination in our population will be of great importance and relevance with reference to the health status of our Nepalese population.

MATERIALS AND METHODS

This is a hospital based comparative cross-sectional study carried out in the Department of Laboratory Medicine (Biochemistry), Psychiatry and Internal Medicine of B P Koirala Institute of Health Sciences, Dharan, Nepal. A total of 40 cases of alcohol abuse with ≥2 score in CAGE questionnaire and matched 40 subjects with no history of alcohol intake were enrolled in the study conducted from October 2015 to September 2016. Informed written consent in understandable language either Nepali or local language was obtained from the participants/attendants. Ethical clearance was taken from the Institutional Review Committee (IRC) BPKIHS, Dharan. The samples of the subjects were taken following the optimum standard protocol and AST, ALT, GGT and ALP was estimated by COBAS 311, Roche Diagnostics analyser following the IFCC recommended guidelines at Biochemistry Laboratory, BPKIHS. CDT was estimated by Enzyme linked Immunosorbent Assay (ELISA). The laboratory assays were standardized and performed identically throughout the process.

The data obtained were entered in Microsoft Excel sheet and analyzed by using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics was used to express demographic data. Bivariate analysis between groups was done using Chi-square for categorical data. ANOVA and Kruskal Wallis with post hoc were used for multiple group analysis. For parametric variables, independent t-test for continuous data and Pearson

correlation coefficient were used to assess the relation between quantitative variables. For non-parametric variables, Mann Whitney U test and Spearman correlation were used. Diagnostic performance was assessed using Receiver Operating Characteristics (ROC) curve. Level of significance of 5%, i.e., 95% confidence interval was considered. Statistical significance was considered at $p \leq 0.05$.

Sensitivity, Specificity and the Positive and Negative Predictive values (PPV, NPV) of %CDT, GGT, AST, ALT, AST/ALT and ALP was obtained using Receiver Operating Characteristics (ROC) curves.

RESULTS

A total of 40 case of alcohol abuse and 40 controls were included in this study. Among the involved participants, majority of them belongs to Hindu (n=44) followed by Kirat (n=16) and then Buddhist (n=20) in religion.

Table 1: Baseline demographic and anthropometric variables and clinical characteristics of study participants.

General Characteristics	Control (n=40)	Case (n=40)	p Value
Age (yrs.)	38.9±14.3	42.5±10.9	0.21
Family Size	4.81±1.81	5.41±1.72	0.08
Weight(kg)	**64.21±9.82**	**57.45±7.91**	**0.001**
Height(m)	1.63±0.068	1.62±0.078	0.12
BMI (kg/m^2)	**24.46±3.21**	**21.62±2.61**	**0.001**
SBP	124±7	127±8	1.22
DBP	76±6	75±6	0.70
Respiratory Rate	16±1	16±2	0.54
Pulse	75±2	74±4	0.59

Independent t Test, p value <0.001 is considered to be significant

There was significantly greater number of married participants in both the case and control groups in this study. Among the alcohol abusers, 87% were found to be smokers.

Table 2: Baseline characteristics of alcohol use in study participants

Characteristics	Groups	Control	Case
Type of alcohol	Local	0	9 (22.5)
	Branded	0	6 (15.5)
	Both	0	25 (62.5%)
Amount of alcohol	<Half (<375 ml)	0	3 (7.5%)
	Half (375 ml)	0	14 (35%)
	>Half (375 ml)	0	23 (57.5%)
Cage Score	0	40 (100%)	0
	1	0	0
	2	0	3 (7.5%)
	3	0	21 (52.5%)
	4	0	16 (40%)
Flushing Response	Yes	0	19 (47.5%)
	No	40 (100%)	21 (52.5%)
Smoking	Yes	0	35 (87.5%)
	No	40 (100%)	5 (12.5%)

The mean duration of alcohol consumption is 19±9 years and minimum and maximum duration are 5 and 43 year, respectively. The 25th percentile is 13 years and 75th percentile showed 22 years.

Table 3: Comparison of Biochemical Parameters in control and case

Biochemical Parameters	Control (n=40)	Case (n=40)	p value
%CDT	2.9±1.2	7.03±1.34	0.001[a]
CDT (mg/dl)	10.59±4.34	17.01±3.61	0.001[a]
AST (U/L)	27.5±7.01	40.10±7.71	0.001[a]
ALT (U/L)	24.47±5.01	31.85±9.18	0.001[a]
ALP (U/L)	172.2±76.8	174.42±68.11	0.334[a]
GGT (U/L)	24.20(16.0, 35.0)	74.0(46.0,123.0)	0.001[b]
AST/ALT	1.14±0.28	1.34±0.37	0.001[a]
Transferrin(mg/dl)	372.51±110.41	250.8±65.8	0.001[a]

[a]= Independent t Test Applied

[b]= Mann-Whitney Test Applied

p value <0.05 is considered to be significant

Alcohol abusing participants have significantly higher levels of serum %CDT, AST, ALT, AST/ALT, Transferrin and GGT as compared to controls ($p<0.001$). But there was no significant difference in serum ALP of case as compared to controls ($p=0.334$), though the levels are increased as compared to the controls as can been seen in the table 3.

Table 4: Serum parameters having different CAGE scores in alcohol abusing cases and controls.

Parameters	Control	CAGE SCORE					
		Two	p value	Three	p value	Four	p value
%CDT	2.9±1.2	7.67±0.83	<0.001[a]	7.05±1.45	<0.001[a]	6.89±1.28	<0.001[a]
AST(U/L)	27.5±7.01	35.0±2.64	0.331[a]	41±7.2	<0.001[a]	39.1±8.65	<0.001[a]
ALT(U/L)	24.5±5.01	22±3.4	0.935[a]	34.9±10.8	<0.001[a]	28.68±4.9	<0.001[a]
GGT(U/L)	24(16,35)	79(16,141	0.17[b]	80(59,106)	<0.001[b]	61.5(42,12)	<0.001[b]
ALP(U/L)	174.4±68.1	198±134.5	0.98[a]	165±71	0.78[a]	165.9±75.6	0.840[a]

[a]ANOVA with multiple comparison with Post Hoc between control and CAGE score two, three and four.

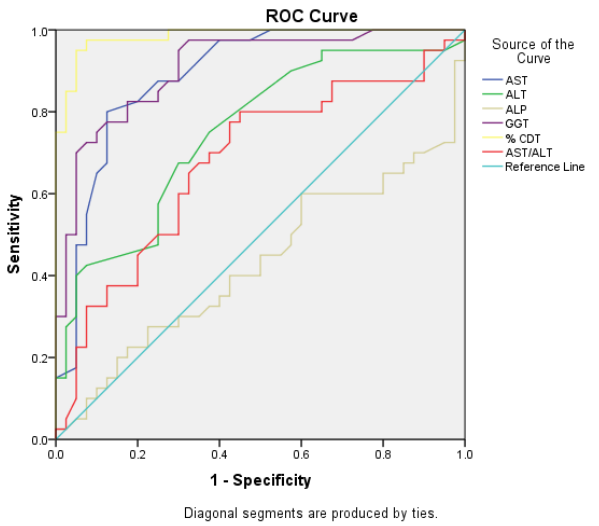

Figure 1: ROC curve of different parameters.

Table 5: ROC analysis of different parameters.

Parameter	Best cut off value	Sensitivity (%)	Specificity (%)	Area under curve
%CDT	3.5%	97	73	0.984
GGT(U/L)	33.5	87	73	0.907
AST(U/L)	33.5	80	87	0.889
AST/ALT	1.1	80	55	0.718
ALT(U/L)	24.5	75	62	0.750
ALP(U/L)	151	60	40	0.429

DISCUSSION

Alcohol consumption is a major health problem in Nepal leading to both serious morbidity and mortality. A community-based study done in Dharan, Nepal found the prevalence of alcohol dependence syndrome to be 25.8% [16] which must have been increased by now. Similarly, another study conducted at BPKIHS for 16 months showed that about 70% women admitted in medical ward are with alcohol related physical problem.[17]

This study has enrolled 40 subjects who were diagnosed to have alcohol abusing behaviour based on the CAGE questionnaire scoring and 40 healthy subjects as controls with comparable age group. The study shows that there is a statistically significant differences between the cases and controls for the parameters namely %CDT, GGT, AST, AST/ALT, ALT but not with ALP. Furthermore, it is observed that %CDT and GGT showed highly significant differences among the groups when compared to the other parameters like AST, ALT, AST/ALT and ALP.

In this study, at a cut off value of 3.5%, CDT has the highest sensitivity of 97% and specificity of 73% followed by GGT and then AST. ALP has the lowest sensitivity and specificity. These findings of the present study are consistent with the other studies. The study by Madhubala suggested that %CDT had higher sensitivity and specificity of 84 and 94%, respectively, followed by GGT with the sensitivity and specificity of 64% and 72%, respectively.[18] The remarkable sensitivity of %CDT when compared to GGT makes it the most specific marker for alcohol abuse. The result of the study in a Han Chinese population demonstrated that CDT is a useful marker to detect heavy alcohol consumption.[15] However, to the contrary, a study by Fagan et al. in 2014 suggested that CDT has limited sensitivity as a biomarker of heavy alcohol consumption.

Considering the highly significant differences between the groups in study and more sensitivity and specificity of %CDT in the study participants compared with the other markers for diagnosing alcohol abuse, the result of this study suggests %CDT as a better marker for early diagnosis of alcohol abuse.

CONCLUSION

Alcohol abusing participants have significantly higher levels of serum %CDT, AST, ALT, Transferrin and GGT as compared to controls ($p<0.001$). Serum %CDT is a better marker both in terms of sensitivity and specificity compared to other conventional markers and thus can be used as a tool to early diagnose the alcoholic cases and monitor the therapy and for early identification of the relapses in alcoholics during treatment.

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