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Usefulness of Biochemical Markers in Alcohol Dependence.

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ABSTRACT

Background: Identification of alcohol dependence is crucial in preventing adverse health effects and social consequences of excessive alcohol consumption. The blood tests used traditionally as markers of excessive drinking are the liver enzymes, gamma glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the red blood cell volume (mean corpuscular volume; MCV). Here, we evaluate the usefulness of these markers, their association with pattern of alcohol consumption and their practical application in management and treatment of alcohol dependent individuals. **Methods:** This was a longitudinal study on 50 alcohol dependent individuals and 50 healthy controls. Detailed information about socio-demographic characteristics and alcohol consumption was recorded through psychiatric interview performa. CAGE questionnaire was applied as a screening tool. Diagnosis of alcohol dependence was confirmed as per ICD-10 criteria. All the subjects underwent laboratory testing for biochemical markers which were estimated by semi automated analyzer. The data thus generated was statistically analyzed by using chi-square test, t-test, ANOVA and Pearson product moment correlation analysis. **Results:** The values for GGT, MCV and AST were significantly high ($p<0.001$) in study group than control group. GGT was found to be significantly related to the amount of alcohol consumption (<0.001). The correlation of GGT was also found to be highly significant with the increasing frequency of alcohol consumption ($r= .488$, $p<0.001$). GGT was found to be most sensitive marker i.e., 64% while HDL-c was found to be having more specificity (100%). Diagnostic accuracy of GGT was found to be highest of all markers(77%). **Conclusion:** These biochemical markers tests are widely available and relatively inexpensive. While having limited sensitivity and specificity in detection of excessive drinking, they also provide valuable data on complications of drinking, comorbid conditions that may be affected by drinking and, in some cases, prognosis.

Keywords: Alcohol dependence, Biochemical markers, Sensitivity, Specificity

INTRODUCTION

Alcohol consumption has been sharing a rising trend all over the world including India, perhaps as a result of newer and greater stress related to rapid changes in life styles. Alcohol dependence is a growing problem and its consequences cost heavily to the community and form a major health problem.

There has recently been considerable speculation about the level of alcohol consumption in India. Various epidemiological surveys have revealed that 20-40% of subjects above 15 years are current users of alcohol and 10% of them are regular or excessive users. One community based survey has reported that alcohol was the primary substance of dependence in 9.9% of urban slum population.[1]

Early identification of alcohol-related problems is important because these problems are prevalent and pose serious health risks to patients and their families.[2-3] Additionally, recent research shows that a brief intervention may be very helpful in decreasing alcohol-related problems or amounts especially in an early phase of the disease.[4-7] Physicians are likely to identify only 20-50% of patients with alcoholism who are attending for medical care.[8-9]

The diagnosis is often based on the patient's self reporting of alcohol consumption, which is very frequently unreliable.[10-11] A host of self report tests have been developed to assist clinical decision making in the treatment of alcohol dependence. Although there are certain advantages of these assessment techniques being their low cost of administration and scoring, and known psychometric properties of validity, reliability and norms but there are potential liabilities of self report measures. In particular, their validity depends on accurate recall and willingness by the client to divulge sensitive personal information. Further, the precise meaning of questions may or may not be understood by the client and even minor changes in wordings may significantly influence the responses. Finally, it is likely, although not yet demonstrated, that feedback based on results from self report measures may be less compelling to clients of the importance of changing their drinking behavior than would be

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feedback based on more objective measures.[12] Many heavy drinkers are in good health, with no apparent ill-effects from their excessive drinking, and are unlikely to seek medical advice,[13] they can skillfully hide their dependence and, when medical advice is finally sought, it is often too late to reverse either the organ damage or the dependence on alcohol. However, if alcohol problems are recognized at an early stage, a physician may be able to prevent their further development and progression.[14-16]

There has been considerable discussion on the impact of alcohol consumption on number of biochemical and hematological measures. As such, biochemical, haematogical and other markers of alcoholism have assumed special significance.[17-18] The search for reliable and valid markers for alcohol dependence is important since the classical clinical approach can pick up early a small proportion of persons with the problem. For these reasons, much effort has been directed towards developing accurate biological markers of alcohol consumption. However, these biochemical tests must be combined with a clinical history (including collaborative history from a relative if possible), physical examination, questionnaires and self reporting. These tests provide objective information regarding alcohol consumption and help the clinician decide on the possible role of alcohol in a clinical problem or disease process. They are also useful in following up an alcoholic patient and provide motivational input to the patient.[19] Laboratory measures of drinking status can enhance the assessment and treatment process in at least four ways: screening, motivational feedback, monitoring relapse and evaluating treatments.[15]

Although numerous studies have been conducted globally, not much research was undertaken in this part of the world where alcohol consumption pattern differs substantially from those found in other countries, either as regards quantity of alcohol ingested or types of beverages consumed, which necessitated to carry out the current study.

The present study was conducted to evaluate the usefulness of biochemical markers such as Gamma Glutamyl Transferase (GGT), Mean Corpuscular Volume (MCV), Serum Aspartate Amino Transferase (AST), Serum Alanine Amino Transferase (ALT), Total Serum Cholesterol (S.Ch), High Density Lipoprotein Cholesterol (HDL-c) and Serum Triglycerides (S.TGs) in alcohol dependent patients attending the outpatient and inpatient department of psychiatry.

MATERIALS AND METHODS

Setting

The study was undertaken in the department of Psychiatry of Guru Gobind Singh Medical College and Hospital, Faridkot (Punjab). The study included fifty male patients attending the outpatient and inpatient department of psychiatry fulfilling the criteria for alcohol dependence and fifty male healthy volunteers (attendants of all patients from outpatient and inpatient department who never or occasionally drink) who were taken as control group. Occasional drinkers are classified as those who drink approximately 20 to 30 grams of alcohol during ceremonies (once or twice in a month, two or three months).

Inclusion Criteria

1. Male patients between 18-65 yrs of age.
2. Patients who opted for written consent for study.
3. Patients consuming alcohol for at least last 2 months.
4. Patients justifying the CAGE questionnaire and ICD-10 criteria for alcohol dependence.

Exclusion Criteria

1. Patients refusing written consent for study.
2. Any psychiatric co-morbidity.
3. Significant medical illness (i.e.liver cirrhosis, tuberculosis, tumor, renal disease, diabetes mellitus etc).
4. Patients consuming any medication such as opiates, salicylates, penicillins, warfarin, aminoglycosides which can affect the activity of biochemical markers.

Tools

1. **CAGE questionnaire:** The CAGE was developed to serve as a brief screening test for significant alcohol problems in a variety of settings. CAGE is an acronym for the four questions that comprise the instrument. Each "Yes" answer is scored as 1, and these are summed to generate a total score. Scores of 1or more warrant follow up, and scores of 2 or more strongly suggest significant alcohol problems.
2. **Psychiatric Interview Performa:** Psychiatric Interview Performa prepared by the department of psychiatry was applied to find out the socio-demographic profile, detailed history including duration, amount and frequency of alcohol intake, general physical and mental status examination.
3. **ICD-10:** The diagnosis of alcohol dependence was made on the basis of international classification of diseases, 10th edition (ICD-10), by World Health Organization.

Procedure

The study was approved by the ethical committee of Guru Gobind Singh Medical College and Hospital. Informed written consent was taken from all subjects under the study. Subjects were divided into two groups – patients fulfilling the criteria for alcohol dependence according to ICD-10 and control group comprising healthy volunteers (attendants of all patients from outpatient and inpatient department of psychiatry) who opted to participate in this study. Each participant in both the groups was asked questions based on CAGE questionnaire. Psychiatric interview Performa was applied to collect data about

socio-demographic profile, detailed history including self reported alcohol consumption, general physical and mental status examination. Alcohol consumption was determined from a questionnaire which inquired into average frequency, duration and amount of alcohol being consumed by the subject. To assess the possible effect of amount of alcohol consumption, alcohol dependent subjects were divided into three subgroups i.e., subjects consuming <60 gms, 60-200gms and >200 gms of alcohol daily.

Laboratory Method

10ml of venous blood was collected from all the subjects under sterile conditions. The values for biochemical markers were measured on the same day. The samples were processed and serum separated as required for analysis. GGT, AST, ALT, S. Cholesterol, HDL-c, S. Triglycerides were estimated by semi automated analyzer.

Statistical Analysis

The data thus generated was subjected to appropriate statistical. Descriptive statistics, in terms of percentage was used to describe the categorical variables. Mean and standard deviation was used to describe various characteristics related to continuous variables. The obtained values were analyzed with the reference values for each biochemical marker. The values obtained for each biochemical marker were further evaluated and compared in both groups. The data and values obtained for each biochemical marker were analyzed by using chi-square test, t-test, ANOVA (one-way analysis of variance)and Pearson product moment correlation analysis (r).

RESULTS

A total of 100 subjects were enrolled in the study. 50 subjects who fulfilled the required criteria for alcohol dependence were included in the study and other 50 healthy individuals constituted the control group. All the subjects were males (100%). Majority of them from the study group belonged to 31-40 years of age group(46%). 32% each have studied upto primary and matriculate level while 16% were graduates. Majority of the subjects from the study group were farmers(50%) hailing from rural areas(64%) and almost all were married(94%). Almost half (42%) have monthly income of more than Rs 20000. All these socio-demographic characteristics were understandable considering this region an agricultural and comparatively prosperous state [Table 1]

Table 1: Socio-demographic characteristics in both groups (n=100)

Variables	Characteristics	Study group		Control group	
		(n)	%age	(n)	%age
Gender	Male	50	100	50	100
Age Distribution (In Years)	≤30	7	14	8	16
	31-40	23	46	22	44
	41-50	15	30	15	30
	51-60	5	10	5	10
Educational Status	Illiterate	10	20	4	8
	Primary	16	32	11	22
	Matriculation	16	32	29	58
	Graduation	8	16	6	12
Prior Employment Status	Farmer	25	50	31	62
	Govt. Servant	10	20	4	8
	Businessman	3	6	3	6
	Retired	1	2	1	2
	Self employed	11	22	11	22
Background	Rural	32	64	35	70
	Urban	18	36	15	30
Marital Status	Single	1	2	4	8
	Married	47	94	44	88
	Divorced	2	4	2	4
Type of Family	Nuclear	25	50	19	32
	Joint	25	50	31	62
Religion	Sikh	40	80	42	84
	Hindu	10	20	8	16
Income (Rs/Month)	≤10000	17	34	10	20
	11000-20000	12	24	18	36
	>20000	21	42	22	44

The CAGE questionnaire was applied to all subjects and cage score wise distribution in both groups was obtained. The score of 3 was found in maximum number of subjects e.g.,22(44%) followed by score of 4 in 20(40%) subjects in study group while score of 0 was found in maximum number of subjects e.g., 40(80%) followed by score of 1 in 10(20%) subjects in control group [Table 2]

[Table 3] makes the comparison of the values obtained for each biochemical marker in both groups using t-test for equality of means. The values obtained were highly significant ($p<0.001$) as far as GGT, MCV and AST were concerned while significant difference was found for the values obtained for ALT ($p=.009$) and S.Cholesterol(.042) in the study group. However, no significant

difference was found for values obtained for HDL-c and S.Triglycerides.

Table 2: Distribution of score according to CAGE questionnaire (n=100)

Cage score	Study group		Control group	
	(n)	%age	(n)	%age
0	0	0	40	80
1	0	0	10	20
2	8	16	0	0
3	22	44	0	0
4	20	40	0	0
Total	50	100	50	100

Table 3: Comparison and evaluation of biochemical marker values of biochemical markers in both groups (n=100) t-test

Biochemical markers	Study group (n=50) Mean (±SD)	Control group (n=50) Mean (±SD)	t-test value	P value
GGT (IU/L)	86.55±81.89	22.51±10.56	5.48	<0.001 (HS)
MCV (Fl)	97.84±12.67	89.77±5.26	4.16	<0.001 (HS)
AST (IU/L)	55.57±45.53	26.80±11.52	4.33	<0.001 (HS)
ALT (IU/L)	41.44±33.87	26.94±18.75	2.64	.009 (S)
S.CHOL-c (mg/dl)	198.52± 59.55	178.86± 31.77	2.06	.042 (S)
HDL-c (mg/dl)	47.43±9.68	45.24±6.98	1.29	.198
S.TGs (mg/dl)	148.58± 57.84	246.88± 708.3	.978	.330

The mean AST: ALT ratio in both groups using t-test for equality of means was calculated. The mean (±SD) ratio in study group and control group was 1.5124(±1.189) and 1.0802(±.313) respectively which was statistically significant (p.015) [Table 4] [Figure 1]. An AST/ALT ratio exceeding 1.5 strongly suggests alcohol-induced liver damage, while a ratio above 2.0 is almost indicative of such a disease.

Table 4: AST: ALT ratio in both groups (n=100) t-test

Biochemical marker	Study group (n=50) Mean (±SD)	Control group (n=50) Mean (±SD)	t-test value	P value
AST:ALT Ratio	1.5124± 1.189	1.0802±.313	2.484	.015(S)

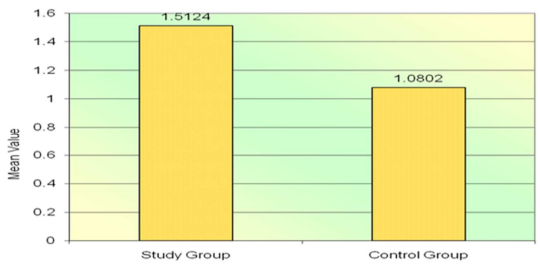

Figure 1: Comparison of Mean AST/ALT ratio in both groups

The association of biochemical markers with quantity of alcohol consumption using one-way ANOVA test was studied. To assess the possible effect of amount of alcohol consumption, alcohol dependent subjects were divided into three subgroups i.e., subjects consuming <60 gms, 60-200gms and >200 gms of alcohol daily.GGT was found to be significantly related to the amount of alcohol consumption (<0.001) while none of other biochemical markers showed any significant correlation [Table 5] [Figure 2].

Table 5: Association of biochemical markers with quantity of alcohol ANOVA test

Biochemical markers	<60gm/day (n=20) Mean (±SD)	60-120gm/day (n=19) Mean (±SD)	>120gm/day (n=11) Mean (±SD)	P Value
GGT (IU/L)	35.08± 23.79	77.43± 28.31	195.86± 108.35	<0.001 (HS)
MCV(Fl)	100.99± 16.34	95.32±8.38	96.50±10.91	.356
AST(IU/L)	56.67±52.83	41.34±15.99	78.14±58.70	.100
ALT(IU/L)	37.25±33.34	34.43±20.29	61.17±47.04	.086
S.Chol(mg/dl)	187.90±71.13	199.11±48.13	216.82±54.75	.441
HDL-c(mg/dl)	45.07±8.47	49.47±10.42	48.18±10.37	.357
S.TGs(mg/dl)	151.70±57.31	154.79±64.30	132.18±48.18	.569

Mean (±SD) quantity of alcohol consumption = 129 ±95.12gm

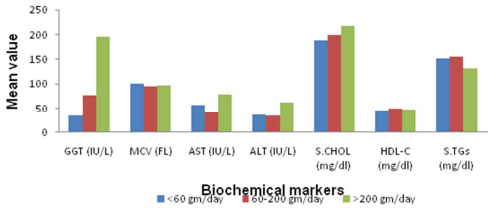

Figure 2: Association of biochemical markers with quantity of alcohol

Table 6: Correlation analysis of biochemical markers with Frequency and Duration of alcohol consumption

Biochemical markers	Frequency		Duration	
	r value	p value	r value	p value
GGT	.488(HS)	<0.001(HS)	.115	.426
MCV	.196	.172	.267	.060
AST	.179	.212	.003	.981
ALT	.153	.289	.051	.726
S.Chol	.197	.171	.004	.981
HDL-c	.027	.85	.124	.390
S.TGs	.095	.513	.097	.503

r =correlation co-efficient

The correlation of biochemical markers with frequency and duration of alcohol consumption and any association thereof was observed. The correlation of GGT was found to be highly significant with the increasing frequency of alcohol

consumption (r= .488, p<0.001) while no other biochemical marker showed any significant correlation with frequency and duration of alcohol consumption [Table 6].

[Table 7] shows the sensitivity and specificity of each biochemical marker.GGT was found to be most sensitive i.e., 64% with specificity of 90% followed by AST i.e., 40% sensitivity and 86% specificity and MCV with 38% sensitivity and 92% specificity respectively.

Table 7: Sensitivity and specificity of biochemical markers (n=100)

Biochemical Markers	True positive	False positive	True negative	False negative	Sensitivity (%)	Specificity (%)
GGT	32	5	45	18	64.00	90.00
MCV	19	4	46	31	38.00	92.00
AST	20	7	43	30	40.00	86.00
ALT	14	4	46	36	28.00	92.00
S.Chol	13	9	41	37	26.00	82.00
HDL-c	3	0	50	47	6.00	100.00
S.TGs	13	12	38	37	26.00	76.00

Further, it is important for physicians to know accuracy of these biochemical markers if these are to be included in management plan of every case of alcohol dependence. In this study, GGT demonstrated better diagnostic accuracy i.e., 77% followed by MCV and AST which showed 65% and 63% diagnostic accuracy respectively [Table 8].

Table 8: Diagnostic accuracy of biochemical markers (n=100)

Biochemical Markers	True positive	False positive	True negative	False negative	Diagnostic Accuracy (%)
GGT	32	5	45	18	77.00
MCV	19	4	46	31	65.00
AST	20	7	43	30	63.00
ALT	14	4	46	36	60.00
S.Chol	13	9	41	37	54.00
HDL-c	3	0	50	47	53.00
S.TGs	13	12	38	37	51.00

DISCUSSION

Our study has examined the usefulness of various biochemical markers and they remain useful adjuncts in the assessment and management of alcohol dependence. The detection of alcohol related problems in a general population remains an important issue as, general physicians fail to recognize most patients with alcohol related problems. They may fail to appreciate the significance of many of the clinical symptoms and findings, which frequently mimic other diseases. These tests provide objective information regarding alcohol consumption and help the clinician decide on the possible role of alcohol in a clinical problem or disease process. Their levels may indicate complications of drinking, or concurrent conditions that may be affected by drinking. They can enhance the assessment and treatment process through screening, monitoring relapse and provide motivational feedback to the patient. GGT and MCV are the most studied and the most widely used among markers of heavy drinking. Sensitivity of combinations may be higher than sensitivity of single tests. In our study, sensitivity of GGT-MCV combination was high in determining alcohol dependency. Further when screening questionnaires like CAGE were combined with these markers, determination rates for alcohol abuse increases.Therefore, these screening tools and biochemical markers hold an important place in the evaluation of existing alcoholism treatment services and must be included as secondary outcome measures in clinical trials of new types of alcohol treatment.

Although the state markers currently in use have value, their limitations and weaknesses make it desirable to develop more sensitive and specific markers. The importance of a marker's precision, accuracy, sensitivity, and specificity cannot be overstated. These markers provide hope for more sensitive and specific aids in diagnosis and improved monitoring for alcohol intake.

Alcohol consumption patterns, like most human behavior, are complex. Clinicians often need to detect patterns of drinking other than the chronic, heavy drinking detected by GGT, MCV, AST, ALT, and other markers. For example, they may need to know whether a person has done any amount of drinking recently or what type of drinking has occurred (e.g., heavy or social drinking). Therefore, finding new biomarkers that measure many different aspects of alcohol consumption will vastly increase the clinician's ability to detect and treat alcohol abuse and dependence. In addition, such biomarkers will help provide more precise definitions of alcohol consumption and alcohol use disorders not only in the clinic but in research where these terms currently are defined less precisely, such as number of drinks consumed over a certain period of time. Finally, more research is necessary before clinically useful trait markers of alcohol dependence are fully developed. The markers first must be validated clinically by testing people before they develop alcoholism and waiting to see how well the marker predicts later behavior. As researchers further develop the markers described here and discover more biomarkers, their work should greatly improve clinician's ability to objectively assess alcohol consumption.

CONCLUSION

These readily available laboratory tests provide important prognostic information and should be integral part of the assessment of the persons with harmful alcohol consumption. In absence of single sensitive and specific marker, the way to improve the detection of alcohol related disorders may be

based upon combined use of screening tools along with biochemical markers. However,the search for ideal biomarkers of alcohol consumption continues.

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