Coexistence of Cardiomyopathy and Chronic Liver Disease in Non-Moderate Drinkers

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ABSTRACT

Introduction: The dose-response relationship suggests a toxic effect of alcohol on heart and liver and the possibility of a correlation between alcohol-induced liver and heart disease. The present study was aimed to look into the relationship between chronic liver and heart muscle disease among the non-moderate drinkers in our context.

Methods: An observational study on non-moderate chronic drinkers was carried out. Clinical evaluation along with detail sonographic study of heart and liver was conducted.

Results: Fifty-eight percent had echocardiographic features consistent with heart muscle disease, either as a dilated cardiomyopathy, categorized by the presence of echo features of impaired LV systolic function and dilated left ventricle or as a possible cardiomyopathy categorized by the presence of any of these two echo features. Similarly, 56 of the total recruits showed ultrasonographic evidence of chronic liver disease as cirrhosis or early cirrhosis. Approximately, 86% of these 56 non-moderate drinkers with chronic liver disease also had echocardiographic features of heart muscle disease and 83% of the 58 non-moderate drinkers showing echo features of heart muscle disease had ultrasonographic features of chronic liver disease.

Conclusions: Our study showed a strongly positive relationship on the coexistence of chronic liver disease and cardiomyopathy among the non-moderate drinkers. Non-moderate drinkers with chronic liver disease have a high likelihood of having a concurrent clinical or sub-clinical heart muscle disease and vice versa.

Keywords: *alcohol; chronic liver disease; heart muscle disease; non-moderate drinking.*

INTRODUCTION

Alcoholic beverages have been used and abused since the dawn of history. In western communities, 90% people drink alcohol once in a life time, 40 to 50% of men have temporary alcohol induced problems and 10 to 20% of men and 3 to 10% of women develop pervasive and persistent alcohol related problems.[1,2]

The effect of alcohol consumption on human health is complex. Although the moderate intake appears to exert a protective effect against coronary heart disease,[3-5] the non-moderate drinking increases overall mortality[6] and morbidity due to cardiovascular diseases.[3] Alcoholism

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is associated with various adverse consequences to health, including hypertension, dilated cardiomyopathy (DCM), arrhythmias and stroke. Long-term alcohol consumption is often complicated by various forms of chronic liver disease (CLD) and heart muscle disease (HMD) including DCM.[7,8] It also has other effects including the increase in cancer risk, adverse interaction with other medications and exacerbation of most medical and psychiatric disorders.

The pathogenesis of these alcohol-induced disorders remains speculative.[9,10] Both CLD,[11] and HMD,[12] have been related to the total lifetime dose of ethanol intake. Alcohol-induced HMD is a group of life style-related cardiovascular disorders caused by excessive alcohol consumption for a long time, where a putative role of alcohol is determinant and alcohol and its metabolites have a direct role in pathogenesis. Alcohol-induced CLD is a group of liver diseases caused by excessive and prolonged intake of alcohol; it might comprise various liver changes such as fatty liver, early cirrhosis and cirrhosis. Because of its multi-factorial origin including obesity, diabetes and other various medical conditions, the fatty liver cannot be solely considered as a condition due to alcohol intake. Nevertheless, these dose-response relationships suggest a toxic effect of ethanol on these tissues and the possibility of a relationship between alcohol-induced disorders of the liver and the heart. Contrary to such expectation, there was an anecdotal perception of an inverse relationship between cirrhosis and cardiomyopathy in chronic alcoholics,[13,14] and it was widely believed that alcoholics who develop cirrhosis are somehow spared from heart disease, and vice versa. However, a number of studies has questioned the inverse relationship between these two complications of alcoholism,[15] and had shown that patients with alcohol-induced cirrhosis do suffer from subclinical or clinical impairment of cardiac function.[16-18]

To investigate this issue, we studied the liver and heart of non-moderate drinkers who were admitted or consulted to the hospital for various medical problems related or unrelated to cardiovascular and gastrointestinal system.

METHODS

This study was conducted during 2010-2011 at a 1050-bedded multispecialty tertiary referral center in central Nepal. Study was approved by the Ethical Committee of the hospital.

Patient Selection: Over a period of one year, 228 non-moderate drinkers were recruited and evaluated out of which only 100 subjects were included in final analysis. Patients were selected from in-patient and outpatient department independent of symptoms. All subjects were Nepalese. No patient objected to being in the study, and all gave informed consent for the non-invasive procedures, data collection and sharing.

Any subjects with non-moderate drinking; i.e. at risk drinking equivalent to a minimum of two standard drinks or 25 gram of ethanol per day (more than two standard drinks per day is equivalent to 250 ml of homemade liquor or 230 ml of non- fortified wine, 86 ml of whisky or vodka) for 10 or more years aged between 35–55 years were included in the study.[19,20]

Subjects with severe hypertension, known rheumatic heart disease, known coronary heart disease, congenital heart disease, advance neurological disorders, chronic kidney disease stage III-V, cor pulmonale and heart failure NYHA IV were excluded from the study. The subjects with a chronic liver disease of known cause except alcohol and subjects with positive serology to HIV, HBsAg, and anti-HCV were excluded from the study. Similarly the subjects with known hypertension, females in peripartum period, seriously ill subjects and subjects with unsatisfactory echo window or incomplete data were also excluded.

Study Protocol: A detailed clinical and social history was obtained and detail clinical examination was carried out to establish a clinical diagnosis. The history of alcohol drinking including types, frequency and average amount were recorded. The current daily intake was considered to be the average of alcohol consumed per day during the last month. Life events such as marriage, military service, festivals and work posts were used as 'anchor points' to assist in recollection (time-line follow-back method).[21] Information regarding signs or symptoms referable to heart or liver disease was also obtained. These data were independently confirmed with family members. The total lifetime dose of ethanol was estimated by adding the total amounts ingested during these anchor points as well. Each subject was taken for detail echocardiographic examination. The presence of chronic liver disease was ascertained by the ultrasonographic examination of liver. For the calculation of daily intake amount and lifetime intake amount of ethanol, the strength of various alcoholic beverages was taken as: beers - 3.4 - 9% v/v, white wine - 8 - 13% v/v, vodka - 37.5 - 57.5% v/v, whisky - 32 - 40% v/v, rum - 32 - 40% v/v.[22]

Heart Disease: Cardiovascular examination was performed in the morning in empty stomach with abstinence of alcohol at least for 12 hours but not more than 24 hours to avoid the acute effects of ethanol on the cardiovascular system and to avoid

the onset of withdrawal features. Apart from routine cardiovascular evaluation with ECG and chest X-ray, detail echocardiographic evaluation with M-mode, 2D and Doppler study including wall motion analysis was carried out to establish structural and functional abnormalities. The mass of the left ventricle was also calculated and interpreted as described elsewhere.[23] All these measurements were performed according to the recommended standards of the American Society of Echocardiography.[24] Diastolic dysfunction was defined as E/A ratio equal or less than one, dilated left atrium (LA) and LV were defined as index more than 2.2 cm/m^2 and 3.2 cm/m^2 respectively.[25] Alcohol-induced heart muscle disease was defined as the conditions causes by chronic consumption of alcohol with echocardiographic features suggestive of DCM or possible DCM. Subjects were labeled as having DCM,[26] in the presence of LVEF < 45% and dilated LV i.e. LVIDd/BSA >3.2 cm/m^2. If there was only one of them, possible DCM was diagnosed.[27] Subjects having other structural changes such as LV hypertrophy, LV diastolic dysfunction and valvular lesions were not included in the HMD as the causative relationship of alcohol and these conditions is not well established.[28]

Liver Disease: Detail clinical and laboratory evaluation including liver function test and serological markers was carried out to reach a clinical diagnosis for the liver condition. Liver condition was assessed mainly based on ultrasonographic (USG) features and classified as normal, fatty liver, early cirrhosis and cirrhosis. Invasive procedures were not used for the diagnosis. Increased liver size more than 12 cm with fatty deposition of various grades was classified as fatty liver and it was not included in alcohol-induced CLD while analyzing final results because of presumed multi-factorial origin of this condition. Alcohol-induced CLD for the analysis purpose was defined as a condition with USG features suggestive of cirrhosis or early cirrhosis; hepatomegaly with coarse echotexture without the features of portal hypertension was labeled as early cirrhosis and decreased liver size or normal liver size with coarse echo texture and the presence of portal hypertension was classified as cirrhosis.

Statistical Analysis: The data obtained were analyzed using statistical software package SPSS 17.0. The mean and standard deviation (SD) of various variables were calculated and expressed as mean ± SD. Parametric and nonparametric tests were used as appropriate. The significance of any differences in means between various groups was tested using F or student's t test. The confidence intervals were calculated at the 95% level. P values <0.05 were considered statistically significant at 5% level and <0.01 at 1% level.

RESULTS

Out of total 228 subjects evaluated only 100 non-moderate drinkers' subjects were included in the data analysis. Out of 128 subjects excluded, 84 subjects had alternative diagnosis for their echocardiographic and USG features other than alcohol. Twenty-four subjects had inadequate USG parameters to comment on liver changes and 20 subjects had poor quality of echo window for satisfactory interpretation (Figure 1). Mean age was 45.1±7.7 years. Two-thirds were male (Table 1).

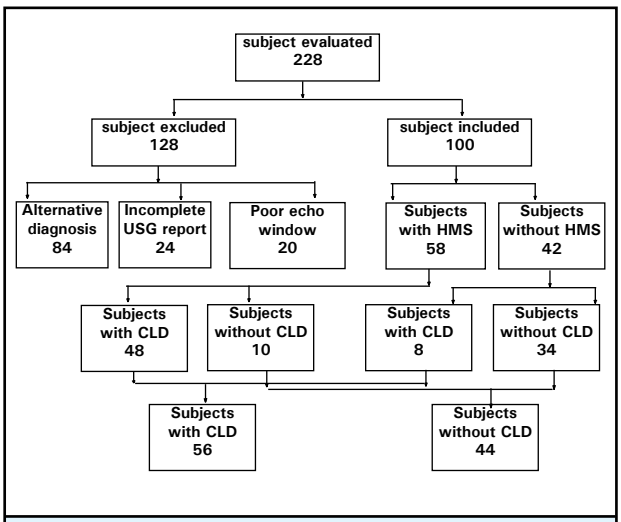

Figure 1. Distribution of study subjects.

Table 1. Characteristics of subjects.

Parameters	Male (n = 68)	Female (n = 32)	Total (n = 100)
Mean age	44.9±8.1	45.6±6.9	45.1± 7.7
Male:Female			2.13:1
Age range (years)	30-55	32-55	30-55
BMI (kg/m^2)	20.9±3.1	23.4±4.8	21.7±3.9
BSA (m^2)	1.6±0.2	1.5±0.2	1.6±0.2
Smoking (%)	68	63	66
Daily alcohol intake (g)	68.7±32.9	56.25±26.43	64.7±22.1
Lifetime intake amount (kg)	575.4±336.7	414.6±234.2	523.9±314.6
Duration of alcohol intake (years)	22.6±7.9	21.1±8.2	22.1±7.9
Lifetime intake range (kg)	91.3-1277.5	175.2-1007.4	91.25-1277.5

Their reported daily intake of ethanol ranged from 25 to 150 g (mean, 64.7 ± 22.1 g)over a period of 22.1 ± 7.9 years. Mean lifetime alcohol amount was 523.9 ± 314.6 kg with a range of 91.2 to 1277.5 kg. The lifetime intake of alcohol was less than 250 kg in 14%, 250-500 kg in 44% and more than 500 kg in 42% alcohol users. Only 32% subjects were symptomatic for cardiovascular symptoms; palpitation and dyspnea in combination were the only specific symptoms significantly associated with impaired LVEF (P <0.05). Other symptoms were equally common in subjects with or without HMD. Similarly only 40% subjects were symptomatic for chronic liver disease. Abdominal distension and gastrointestinal bleeding were the only specific symptoms significantly associated with the presence of CLD (P <0.01). Fifty-eight percent and 56% alcoholic subjects had HMD and CLD respectively with almost similar rate among male and female, with a trend to lower value of lifetime intake amount of alcohol (575.4 ± 336.9 vs 414.6 ± 234.2 kg) in women.

In an analysis where a comparison was made between the subjects with CLD (subjects with USG features suggestive of cirrhosis and early cirrhosis) and the subjects without CLD (subjects with USG features suggestive of normal or fatty liver), significantly higher amount of daily intake alcohol (79.5 vs 45.9 g/day, P <0.001), duration (24.3 vs 19.5 years, P <0.05) and total lifetime intake amount (694.3 vs 307.2 kg, P <0.001) was observed in CLD and without CLD subjects respectively. Similarly the CLD group had low mean LVEF (40 vs 58%, P <0.001) and the high incidence of HMD (86 vs 23%, P <0.001) (Table 2).

Table 2. Various drinking parameters in subjects with CLD and without CLD.

Parameters	CLD (n = 56)	No CLD (n = 44)	P value
Age	45.9 ±6.2	44.2 ± 9.4	NS
M:F	2.22:1	2:1	NS
Daily intake of alcohol (g/day)	79.5 ± 30.3	45.9 ± 21	<0.001
Duration of alcohol intake (years)	24.25 ± 6.6	19.5 ± 8.8	<0.05
Lifetime intake amount (kg)	694.3 ± 299.3	307.2 ± 166.6	<0.001
HMD (%)	86	23	<0.001
LVEF (%)	39.8 ± 10.9	58.2 ± 7.9	<0.001
Impaired LVEF (%)	64	9	<0.001
LVM Index (kg/m^2)	121.0 ± 27.8	95.4 ± 26.4	<0.001
Increased in LVM (%)	57	32	NS
Diastolic dysfunction (%)	36	59	NS
Dilated LV (%)	82	14	<0.001
Dilated LA (%)	75	12	<0.001
Regurgitations (%)	75	18	<0.001

NS – not significant (P >0.05)

In another analysis, the drinking parameters, ultrasonographic features of liver and liver function tests of subjects with HMD were compared with that of without HMD (Table 3).

Table 3. Various parameters among subjects with HMD and without HMD.

Parameters	HMD (n = 58)	No HMD (n = 42)	P value
Age (years)	47.7±5.9	41.6±8.4	<0.01
M:F	20:9	14:7	NS
Daily intake of alcohol (g/day)	78.6±31.3	45.5±18.3	<0.001
Duration of alcohol intake (years)	25.5±7.0	17.52±6.7	<0.001
Lifetime intake amount (kg)	706.1±289.2	272.4±101.5	<0.001
CLD (%)	83	19	<0.001
AST/ALT >2 (%)	40	50	NS
Serum albumin level (g/dl)	2.69±0.9	3.2±0.9	<0.05
Decreased albumin level (%)	82	55	<0.05
Prothrombine time (min)	4.9±3.0	5.3±4.1	NS
Raised prothrombine time (%)	62	50	NS

NS – not significant (P >0.05)

The duration, daily intake, and life time intake amount of alcohol were significantly higher among subjects with HMD (25.5 vs 17.5 years, P<0.05, 78.6 vs 45.6 g/day, P <0.001 and 706.1 vs 272.4 kg, P<0.001 respectively). The proportion of subjects with CLD was high among HMD subjects (83 vs 19%, P<0.001). Markers of acute liver damage were raised in both groups, but the statistically significant difference was not seen. However, the markers more reflecting chronic liver disease such as the serum albumin were significantly lower among subjects with HMD. Nearly 82% subjects with HMD in comparison to 55% subjects without HMD had decreased albumin level (P <0.001). The prothrombine time was also raised in both groups but there was no significant difference among them.

DISCUSSION

This is the first of its kind study from Nepal. The results of our study are also at variance with the past-held view of an inverse relationship between cirrhosis and cardiomyopathy in chronic alcoholics,[13,14] and supports alternative views on this regard.[15-18] Majority of the alcoholics (56%) had chronic liver disease in the form of cirrhosis or early cirrhosis, remaining had either fatty liver or normal liver, whereas 58% alcoholics suffered from HMD in the form of DCM or possible DCM. The results of this study clearly indicate that HMD and CLD not only may coexist, but that they often do so. In one side, more than 85% subject with CLD also had HMD; in another side more than 82% subjects with HMD also had CLD. In contrast to this, only 19.05% alcoholic subjects without HMD had CLD and only 22.72% subjects without CLD had HMD. These data also suggest that alcoholics who are relatively resistant to the effects of chronic alcohol intake on the heart also manifest some degree of resistance in the liver as well.

In our study the cardiac dysfunction was common in patients with CLD, and more than 85% subjects with chronic liver disease had evidence of dilated cardiomyopathy or possible DCM. The possibility of cardiac impairment as a secondary effect of chronic liver disease can also be raised, but it seems very unlikely. Estruch et al,[29] had studied the cardiac function in non-alcoholic cirrhosis and had found entirely normal cardiac function in all non-alcoholic cirrhotic subjects. They also showed that the alcoholics with normal cardiac function who had been drinking large amounts of ethanol had a much lower incidence of cirrhosis than did similar patients with documented alcohol-induced heart muscle disease.

The demonstration of higher rates of DCM and possible DCM in patients with CLD is in accord with previous studies that have shown preclinical cardiac dysfunction or latent cardiomyopathy in chronic alcoholics with liver disease.[16-18,29-32] Indeed, the low systemic vascular resistance, especially in cirrhotic with ascites,[33] may mask the signs of cardiac dysfunction, which may be apparent when the vascular resistance is increased towards normal,[30] or when the patient is subjected to volume or pressure overload.[16] In our study, significant number of alcoholic subjects also had left ventricular diastolic dysfunction which was more common among the subjects without CLD. Its incidence had decreased among subjects with CLD where the incidence of LV

systolic dysfunction was high. This could be because of the pseudonormalization of diastolic function when the systolic dysfunction is present.[22]

Although the pathogenesis of HMD including DCM,[9] and CLD including cirrhosis,[10] has not been clearly defined, the correlation between cardiac and liver diseases on the one hand and the dose-response relationship between these disorders and ethanol consumption on the other,[11,12] suggest the possibility of a common pathogenetic mechanism at the cellular level. Cardiovascular death is an important cause of mortality in alcoholics.[34] In view of the substantial prevalence of cardiomyopathy in alcoholics with liver disease, the occurrence of sudden death in alcoholics with cirrhosis or fatty liver,[35,36] likely reflects an increased susceptibility to fatal arrhythmias.

Some of the cardiovascular abnormalities in our alcoholic subjects can also be a part of cirrhotic cardiomyopathy, a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response to physiologic, pathologic, or pharmacologic stress.[37,38] It is difficult to delineate which abnormalities are the part of DCM and which the part of cirrhotic cardiomyopathy. Although this was the beyond the scope of our study, we assume that few of the findings could also be the part of cirrhotic cardiomyopathy in some subjects and this issue needs on further clarification and studies.

This study has some limitations; most of them were inherent to its descriptive nature. In addition, the sample size was very small and all the subjects were alcoholics only; the conclusion on the extent of echocardiographic abnormalities in non-alcoholic chronic liver disease cannot be derived. Similarly we do not know the incidence of these studied parameters such as DCM and chronic liver disease in normal population. Therefore, few of the conditions in liver and heart may not be fully related to alcohol intake only or can also be a part of cirrhotic cardiomyopathy. Moreover, our study of alcoholic liver diseases and its classification is solely dependent on ultrasonographic parameters only and may not be acceptable to all.

CONCLUSIONS

A relationship exists between HMD and CLD. Non-moderate drinkers with HMD have a higher prevalence of symptomatic and non-symptomatic CLD. Similarly non-moderate drinkers with CLD show higher rates of symptomatic or asymptomatic HMD. In other hand, alcoholic subjects free from either heart or liver disease are more likely to be free from toxic effects in another organ too. Therefore, despite unknown pathogenesis of HMD and CLD, the coexistence of cardiac and liver diseases on the one hand and the dose-response relationship between these disorders and alcohol consumption on the other, suggest the possibility of a common pathogenetic mechanism at the cellular level. This study, despite its observational nature and small size, is clearly successful to show the concurrent existence of HMD and CLD in alcoholic subjects. A more precisely designed prospective study with large sample size will be crucial for further clarification and strengthening the results of present study.

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