Can Alcoholic Liver Disease and Nonalcoholic Fatty Liver Disease Co-Exist?

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Background: Nonalcoholic fatty liver disease (NAFLD) by definition would require exclusion of significant alcohol intake. Present study was aimed to assess the prevalence of various components of metabolic syndrome (MS) in patients with alcoholic cirrhosis (AC) and to study the affect of its presence on the severity of liver disease, testing the hypothesis if alcoholic liver disease (ALD) and NAFLD could co-exist. **Methods:** In a retrospective analysis of 16 months data, 81 patients with AC were analysed for the prevalence of MS. The diagnosis of AC was based on the history of alcohol intake, clinical examination, serum biochemistry, hemato-logical parameters, exclusion of other causes of chronic liver disease, imaging and upper gastrointestinal endoscopy. Severity of liver disease was assessed by Child-Turcotte-Pugh (CTP) score. MS was assessed as per the ATP III criteria and the affect of MS on CTP score was evaluated. **Results:** All 81 patients with AC were male [mean age 50.9 ± 9.5 , mean CTP score 8.38 ± 1.66]. But for three patients (3.7%) all other 78 patients (96.3%) with AC had at least one component of MS. Forty-three (53.0%) patients had full blown MS with three or more components of MS. Sixty-one (75.30%) patients were either overweight [22 (27.1%)] or obese [39 (48.1%)], with a mean BMI of $25.35 \pm 3.86 \text{ kg/m}^2$. Type II DM was present in 40 (25%) and 28 (34.5%) patients were hypertensive. Twenty-two (27.2%) patients had hypertriglyceridemia and 52 (64.2%) had low HDL. Eleven (13.6%) patients had Child's A cirrhosis, 46 (56.8%) had Child's B and 24 (29.6%) patients had Child's C cirrhosis. Even though not significant statistically, patients with Child's C cirrhosis (17, 70.83%) had higher presence of MS in comparison to Child's A (7, 63.6%) and B (19, 41.3%) cirrhosis. **Conclusion:** MS is common in patients with AC. Presence of MS may be contributing towards severity of liver disease in these patients indirectly suggesting the co-existence of ALD and NAFLD. (J CLIN EXP HEPATOL 2017;7:121-126)

The metabolic syndrome (MS) is a combination of several cardiovascular risk factors including central obesity, elevated blood pressure, fasting glucose and triglyceride levels and low concentration of high density lipoprotein (HDL).¹ It is believed to occur secondary to several factors including sedentary lifestyle, inappropriate diet and genetic predisposition.² Though linked closely to nonalcoholic fatty liver disease (NAFLD), individual components of MS may be affected by alcohol consumption. In the present study, we hypothesized that alcohol consumption might increase the risk of developing MS in patients with alcoholic cirrhosis (AC) and its presence might affect the severity of liver disease by causing an additional insult of NAFLD.³

Keywords: nonalcoholic steatohepatitis, NASH, fatty liver, metabolic syndrome, cirrhosis

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Abbreviations: AC: alcoholic cirrhosis; BMI: body mass index; CTP: Child-Turcotte-Pugh; DM: diabetes mellitus; HDL: high density lipoprotein; IFG: impaired fasting glucose; MS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; TGs: triglycerides

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PATIENTS AND METHODS

Definition of alcoholic cirrhosis

In a retrospective analysis of 16 months data (January 2012 to April 2013), 81 patients with AC, diagnosed on the basis of amount and duration of alcohol intake ($\geq 80 \text{ g/day}$ for more than 10 years), clinical examination, serum biochemistry (elevated bilirubin, $\text{AST} > \text{ALT}$, low albumin), hemato-logical parameters (low platelets, deranged INR), imaging (heterogenous liver with irregular outline, with or without dilated portal vein, splenomegaly, ascites and collaterals), upper gastrointestinal endoscopy (evidence of oesophago-gastric varices and/or portal hypertensive gastropathy) and exclusion of other causes of chronic liver disease were included in the study. Patients with both compensated and decompensated cirrhosis were included and those with acute-on-chronic liver failure (ACLF) and hepatocellular carcinoma were excluded from the study. Patients who were actively consuming alcohol in the 3 months prior to study enrolment were also excluded from the study.

Anthropometry

All patients were subjected to a detailed anthropometric examination and overweight and obesity were defined as per the Asia Pacific criteria.⁴ Because of the presence of ascites in patients with decompensated cirrhosis, body mass index (BMI) (modified as per Asia Pacific criteria)

was used as a surrogate marker for central obesity (waist circumference) in all patients. Height in cm using a calibrated scale and body weight in kg using a common bathroom scale were measured to the nearest 0.1 cm and 0.1 kg respectively without shoes. The excessive weight contributed by the presence of ascites was deducted (mild ascites: 2.2 kg, moderate: 6 kg, severe: 14 kg) and BMI (body weight [kg]/height [m]²) was calculated.⁵ Overweight was defined as a BMI ≥ 23 but <25 kg/m², class I obesity as BMI ≥ 25 kg/m² but <30 kg/m² and class II obesity as BMI ≥ 30 kg/m².

Investigations

Fasting blood samples (after 10–12 h of overnight fast) were collected from the antecubital vein to measure serum concentration of glucose, total cholesterol, triglyceride (TG), HDL, low density lipoprotein (LDL). A fasting blood sugar (FBS) of ≥ 110 and <126 mg/dL was taken as impaired fasting glucose (IFG) whereas an FBS ≥ 126 mg/dL was defined as diabetes mellitus (DM). Liver function tests (serum bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total protein and albumin) were also done in all patients using the fasting sample at the random access autoanalyser (Modular-P, Roche Diagnostics, Germany). All patients were also subjected to a complete hemogram (Hb, TLC, DLC, platelets) and coagulogram (PT, PTL, INR and APTT) using an autoanalyser and all patients were screened for HBsAg and anti-HCV (SD HBsAg and Anti-HCV ELISA, Bio standard diagnostics, Gurgaon, India). Other etiological work up like anti-HBc (total), autoimmune markers, iron profile, serum ceruloplasmin and celiac serology were done if clinically indicated. All patients were also subjected to an abdominal ultrasound and an upper gastrointestinal endoscopy was done in all patients at the baseline.

Metabolic Syndrome

MS was defined as presence of 3 or more of the following 5 risk factors as per the National cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)-III criteria.⁶ As mentioned earlier, because of the presence of ascites in patients with decompensated cirrhosis, BMI was used as a surrogate marker for central obesity in all patients.

- (1) Class I obesity as BMI ≥ 25 kg/m² but <30 kg/m² and class II obesity as BMI ≥ 30 kg/m².
- (2) Serum triglyceride >150 mg/dL.
- (3) Serum HDL cholesterol <40 mg/dL for men and <50 mg/dL for women.
- (4) Systolic/diastolic blood pressure $>130/85$ mmHg or known hypertensive.
- (5) Fasting plasma glucose >110 mg/dL or known diabetic.

Statistical Analysis

All statistical analysis was performed using SPSS software (version 22, SPSS Inc., Chicago, IL, USA) Mean and standard deviation was used for continuous variables whereas frequency and percentages was used for discrete data. For comparison of frequencies, Chi-Square Test was used. For comparison of continuous variables, ANOVA (analysis of variance) was used and post hoc analysis by least square difference (LSD) method was employed to compare the means of individual groups. *P* value was set at a significance of 0.05.

RESULTS

All 81 patients with AC included in the study were male (mean age of 50.92 ± 9.5 years) (Table 1). Sixty-one (75.30%) patients were either overweight [22 (27.2%)] or obese [class I obesity *n* (14.8%), class II obesity 39 (48.1%)], with a mean BMI of 25.35 ± 3.86 kg/m². Fifteen (18.5%) patients had IFG whereas twenty-five (30.8%) had type II DM and twenty-eight (34.5%) patients were hypertensive. Dyslipidemia in the form of low HDL was seen in fifty-two (64.2%) and twenty-two (27.2%) patients had elevated TG (Table 2).

But for three patients (3.7%) all other 78 patients (96.3%) with AC had at least one component of MS. The prevalence of full blown MS with ≥ 3 components of ATP III criteria was present in 43 (53.0%) patients with two components present in 18 (22.2%), 3 components in 25 (30.8%), 4 components in 15 (18.5%) and all five components in 3 (3.7%) patients (Table 2).

Table 1 Showing the Baseline Characteristics of Patients with Alcoholic Cirrhosis.

Parameters	N = 81
Age	50.92 $\pm$ 9.5
Sex (M:F)	81:0
AST (IU/ml)	75.40 $\pm$ 69.39
ALT (IU/ml)	51.17 $\pm$ 57.62
Bilirubin	3.8 $\pm$ 7.6
AST	75.40 $\pm$ 69.39
ALT	51.17 $\pm$ 57.62
Albumin	3.3 $\pm$ 1.02
CTP A	11 (13.58%)
CTP B	46 (56.79%)
CTP C	24 (29.62%)
Mean CTP Score	8.38 $\pm$ 1.66

CTP: Child–Turcotte–Pugh.

AST: aspartate aminotransferase.

ALT: alanine aminotransferase.

Table 2 Showing the Metabolic Syndrome and Its Components in Patients with Alcoholic Cirrhosis.

Parameters	No. and Prevalence (%)
Anthropometry	
Normal weight (BMI >18 to < 23)	20 (24.69%)
Overweight (BMI >23 to < 25)	22 (27.16%)
Class I obese (BMI >25 to < 30)	27 (33.3%)
Class II obese (BMI >30)	12 (14.81%)
Lipid profile	
Elevated TGs	22 (27.16%)
Low HDL	52 (64.19%)
Metabolic syndrome	
0 parameter	3 (3.7%)
1 parameter	17 (20.98%)
2 parameters	18 (22.22%)
3 parameters	25 (30.86%)
4 parameters	15 (18.51%)
5 parameters	3 (3.7%)
Metabolic syndrome (≥ 3 components)	43 (53.08%)
Impaired fasting glucose	15 (18.5%)
Diabetes mellitus (DM)	25 (30.86%)
Hypertension (HTN)	28 (34.56%)

BMI: body mass index.

Most of the patients were in Child–Turcotte–Pugh (CTP) class B (46, 56.8%) followed by class C (24, 29.6%) and class A (11, 13.6%) with a mean CTP score of 8.38 ± 1.6 (Table 1). Even though the presence of MS was higher in patients with Child's C cirrhosis (17, 70.83%) in comparison to Child's A (7, 63.6%) and B (19, 41.3%), the difference was not significant statistically ($f = 0.732$, $P = 0.602$) (Table 3). In addition, there was no difference in the presence of different components of MS amongst different Child's classes of cirrhosis (Table 3, Figures 1–4).

DISCUSSION

The link between MS and NAFLD is well known^{7,8} but the prevalence of MS and its components among patients with AC is not well studied. Our study demonstrates a high prevalence of MS in patients of AC (53.0%) which clearly exceeds the prevalence of MS in general population (33.5%)

Figure 1 Presence of abnormal BMI amongst different CTP classes of alcoholic cirrhosis.

in India.⁹ Various metabolic alterations occur in patients with cirrhosis liver. Patients with cirrhosis tend to develop glucose intolerance due to secondary hyperinsulinemia; they also tend to lose weight because of poor nutrition and the hyper-catabolic state. They also have reduction in serum levels of lipids because of poor synthesis and have fall in blood pressure because of splanchnic vasodilatation and reduction in mean arterial pressure. But for DM, other components of MS thus tend to decrease in patients with advanced cirrhosis. The fact that our patients with AC had higher prevalence of MS would suggest a causal link between alcohol and MS. In a study from Japan, it was shown that excessive intake of ethanol (>20 g/day) is associated with an increased prevalence of MS when compared to average drinkers (22% vs 13.9%). It was suggested that excessive alcohol consumption increased the visceral fat accumulation and resulted in the development of MS in this subset of patients.¹⁰ In a study by Freiberg et al. it was noted that subjects who consumed 1–19 and ≥ 20 drinks of alcohol per month had increased odds ratios (ORs, 0.65 and 0.34) for the prevalence of the MS compared with current non-drinkers ($P < 0.05$).¹¹ Same study also found that alcohol consumption was significantly associated

Table 3 Showing the Presence of Metabolic Syndrome Components As Per the CTP Score of Cirrhosis.

Metabolic components	0	1	2	3	4	5
CTP A (11 Patients)	1 (9.09%)	1 (9.09%)	2 (18.18%)	3 (27.27%)	3 (27.27%)	1 (9.09%)
CTP B (46 patients)	2 (4.34%)	13 (28.26%)	12 (26.08%)	11 (23.91%)	7 (15.21%)	1 (2.17%)
CTP C (24 patients)	0	3 (12.5%)	4 (16.66%)	11 (45.83%)	5 (20.83%)	1 (4.16%)

CTP: Child–Turcotte–Pugh.

Figure 2 Prevalence of impaired fasting glucose (IFG), diabetes mellitus (DM) and hypertension (HTN) amongst different CTP classes of alcoholic cirrhosis.

Figure 3 Prevalence of elevated triglycerides and low HDL amongst different CTP classes of alcoholic cirrhosis.

with the prevalence of low serum HDL cholesterol, elevated serum TG and a high waist circumference.¹¹ In another study from Korea, it was established that all individual components of the MS were significantly associated with heavy drinking (>30 g/day).¹ Studies have also documented higher risk of DM and hypertension with excessive alcohol intake.^{12,13} It has also been shown that alcohol consumption can worsen blood sugar control in patients with already established DM.¹⁴

The type of alcoholic beverage consumed also has an impact on metabolic parameters and it was shown by Rosell et al. that subjects who consumed moderate amounts of wine exhibited a more favorable pattern of metabolic profile when compared to subjects with predominant consumption of spirits.¹⁵ Increased risk of type II DM was documented in men who consumed >21 drinks/

week when compared to men who had ≤ 1 drink/week and the increased risk of DM was predominantly related to consumption of spirits rather than to beer or wine.¹⁶ All our patients with AC consumed spirits and none used to consume wine which can partly explain the high prevalence of MS in our subset of patients.

Alcohol is linked to an increased prevalence of MS in several ways. Consuming moderate amount of alcohol has been shown to be associated with visceral distribution of fat¹⁷ which is a well known predictor of insulin resistance.¹⁸ Alcohol consumption also leads to increase in plasma VLDL with or without chylomicronemia which is responsible for causing hypertriglyceridemia.¹⁹ Chronic alcoholism is also known to cause impaired glucose tolerance as it may lead to reduced insulin binding and inhibition of intracellular signaling related to that of insulin.²⁰

Figure 4 Prevalence of MS and its components across amongst different CTP classes of alcoholic cirrhosis.

Although our study demonstrated a higher prevalence of MS in patients of AC belonging to CTP class C when compared to class A and B, this did not achieve statistical significance in view of the small sample size across each group. This finding can partly be explained by the advanced liver dysfunction in patients with Child's C cirrhosis leading to an altered lipid and glucose metabolism. A hypothetical explanation for increased severity of liver disease in patients with AC and MS could be co-existence of alcoholic liver disease (ALD) and NAFLD. Even though small amount of alcohol intake may provide protection against NAFLD; this protection disappears with excess intake of alcohol. Thus, consuming excessive amount of alcohol may put patients with AC at risk of developing liver disease not only from alcohol but also from the MS induced NAFLD.²¹ Even though NAFLD by definition would occur in the absence of significant alcohol intake, our study is perhaps one of the first studies not only demonstrating the prevalence of MS in patients of AC but also suggesting that both ALD and NAFLD can co-exist and may contribute toward the severity of liver disease.

The strengths of the present study include (i) an adequate assessment of the prevalence of MS and its components in patients with AC. (ii) Stratification of patients based on CTP scores. (iii) Suggesting a possible link between MS and severity of liver disease amongst patients with AC. The study is however limited by its retrospective design and small sample size. Cirrhotic patients inherently have an altered lipid profile and impaired glucose metabolism which can affect the prevalence of MS in this subset of patients. Many of our patients had ascites and we have tried to overcome the fallacy of measuring an inappropriate waist

circumference in these patients by using BMI as a surrogate marker adjusting it for the presence of ascites.

CONCLUSION

In conclusion, the results of this study indicate that MS is common in patients with AC and presence of MS may be contributing to the pathogenesis and disease progression in these patients possibly by the co-existence of ALD and NAFLD. Further studies including a larger sample size are needed to confirm these findings.

CONFLICTS OF INTEREST

The authors have none to declare.

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