

# Metabolic Derangement in Acute and Chronic Liver Disorders

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## Abstract

**Aims:** This study aims to assess glycemic and lipid derangement in acute and chronic liver disorders. **Materials and Methods:** A cross-sectional study was conducted on 104 patients diagnosed with acute or chronic liver disorder. Acute liver disease (ALD) patients were 40 and chronic liver disease (CLD) patients were 64. **Results:** The mean value of fasting plasma glucose (FPG) in patients with ALD was  $91.8 \pm 5.4$  mg/dl and in CLD was  $115.7 \pm 17.9$  mg/dl, the difference was significant. The mean value of A1c was  $4.3 \pm 0.6$  in ALD and  $6.1 \pm 0.8$  in CLD, the difference was significant. In patients with CLD mean cholesterol was higher  $177.4 \pm 28.8$  mg/dl when compared to ALD  $140 \pm 35.1$  mg/dl, but the difference was not significant. ALD patients' high-density lipoprotein (HDL) was  $50.4 \pm 5.1$  mg/dl, and in CLD patients, HDL was  $44.4 \pm 6.1$  mg/dl. In CLD mean triglyceride (T) was  $148.9 \pm 6.4$  mg/dl while in ALD T was  $134.8 \pm 14.2$  mg/dl, the difference was significant. **Conclusions:** CLD is associated with glycemic derangement demonstrated by deranged FPG and A1c. In patients of ALD, no metabolic derangement was observed.

**Keywords:** A1c, acute liver disease, chronic liver disease, metabolic derangement

## INTRODUCTION

The liver plays a central role in carbohydrate, lipid and amino acid metabolism and is also involved in metabolizing of drugs and environmental toxins. Liver injury may be either acute or chronic.<sup>[1]</sup> The metabolic dysregulation associated with diabetes mellitus (DM) causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual as well as the health system.

Up to 96% of patients with cirrhosis may be glucose intolerant, and 30% may be clinically diabetic.<sup>[2]</sup> Currently, it is a matter for debate whether type 2 DM (T2DM), in the absence of other risk factors contributing to metabolic syndrome (obesity and hypertriglyceridemia), could be a risk factor for the development and progression of liver disease.<sup>[3]</sup> The liver has an important role in carbohydrate metabolism since it is responsible for the balance of blood glucose levels by means of glycogenesis and glycogenolysis. In the presence of hepatic disease, the metabolic homeostasis of glucose is impaired as a result of disorders such as insulin resistance (IR), glucose intolerance, and diabetes. IR occurs not only in muscular tissue, but also in adipose tissue, and this combined with hyperinsulinemia seem to be important pathophysiologic bases of diabetes in liver disease.<sup>[4]</sup>

In addition, the etiology of liver disease is important in the incidence of DM, since nonalcoholic fatty liver disease (NAFLD), alcohol, hepatitis C virus (HCV), and hemochromatosis are frequently associated with DM. DM in patients with compensated liver cirrhosis may be subclinical, since fasting serum glucose levels may be normal. IR in muscular and adipose tissues and hyperinsulinemia seem to be the pathophysiologic basis of diabetes in liver disease. An impaired response of the islet  $\beta$ -cells of the pancreas and hepatic IR are also contributory factors. NAFLD, alcoholic cirrhosis, chronic hepatitis C (CHC), and hemochromatosis are more frequently associated with DM. IR increases the failure of the response to treatment in patients with CHC and enhances the progression of fibrosis. DM in cirrhotic patients may be subclinical. Hepatogenous diabetes is clinically different from that of T2DM since it is less frequently associated with microangiopathy and patients more frequently suffer complications of cirrhosis. DM increases the mortality of cirrhotic patients.<sup>[5]</sup>

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## MATERIALS AND METHODS

With the permission of the Institutional Ethics Committee, cross-sectional study was conducted on patients  $\geq 18$  were already diagnosed with acute or chronic liver disorder attending outpatient and inpatient department of our tertiary care center at Allahabad, India. Patients already diagnosed with DM, thyroid disorders, chronic pancreatitis, chronic ingestion of steroids, pregnancy were excluded from the study. History included the duration of disease, any drug intake, and any concurrent or chronic illness. The laboratory tests included complete blood count, A1c, fasting plasma glucose (FPG), prandial plasma glucose (PPG), liver function tests, hepatitis B virus surface antigen (HBsAg), anti-HCV, HIV, prothrombin time, international normalized ratio, fasting lipid profile, serum urea, serum creatinine, urine micral test, fundus examination, and ultrasonographic assessments. Fatty liver was diagnosed by ultrasonography if, the echogenicity of the normal liver equals or minimally exceeds that of the renal cortex or spleen, intrahepatic vessels are sharply demarcated, and posterior aspect of the liver are well depicted, fatty liver may be diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture. Criteria for the diagnosis of DM<sup>[6]</sup> were symptoms of diabetes plus random blood glucose concentration  $\geq 200$  mg/dl or FPG  $\geq 126$  mg/dl or A1c  $\geq 6.5\%$  or 2-h plasma glucose  $\geq 200$  mg/dl during an oral glucose tolerance (IGT) test.

A total of 104 cases, 40 cases of acute liver disease (ALD) and 64 cases of chronic liver disease (CLD) were enrolled and screened for metabolic derangements. Out of 104 subjects studied, 84 were male and 20 females. Data were compiled and analyzed using GraphPad Prism Software Inc., Version 6.0 (San Diego, California, USA) with the level of significance being 0.05.

Numerical data were analyzed using paired and unpaired Student's *t*-test and *z*-test for proportions.

## RESULTS

Mean age was  $45.9 \pm 12.4$  (years) with a range between 20 and 62 years. A total of 104 cases, 40 cases of ALD and 64 cases of CLD were enrolled and screened for metabolic derangements. Etiology of ALD and CLD cases is listed in Table 1.

Out of forty patients of ALD, none had deranged FPG. Out of 64 patients of CLD 26 (41%), patients had diabetes, and 16 had impaired FPG. Out of forty cases of ALD, none had PPG above 140 mg/dl. Out of 64 cases of CLD 14 (21%)

had PPG between 140 and 199 mg/dl and 26 (39%) had PPG above 200. Out of forty patients of ALD, none had A1c above 5.6. Out of 64 patients of CLD, 26 (60%) patients had A1c above 6.5. Table 2 shows a comparison of parameters between ALD and CLD patients.

The mean FPG patients of hepatitis B were  $118 \pm 23.8$  mg/dl and in patients of hepatitis C was  $109 \pm 18.2$  mg/dl.

It was comparatively higher in patients of hepatitis B, but the difference was statistically insignificant. The mean PPG patients of hepatitis B were  $180.1 \pm 57.9$  mg/dl and in patients of hepatitis C was  $165.2 \pm 38.9$  mg/dl. It was comparatively higher in patients of hepatitis B, but the difference was statistically insignificant. The mean A1c patients of hepatitis B was  $5.9 \pm 0.7$  and in patients of hepatitis C was  $5.8 \pm 0.7$ . It was comparatively higher in patients of hepatitis B, but the difference was statistically insignificant.

Table 3 shows a comparison between lipid profile of ALD and CLD cases. Triglyceride (TG), cholesterol, low-density lipoprotein (LDL) levels were higher, and high-density lipoprotein (HDL) levels were lower in CLD cases when compared to ALD (significant).

## DISCUSSION

Correlation of FPG and PPG with ALD and CLD showed a significant increase in CLD cases. This observation is similar to the study done by Ennaifer *et al.*<sup>[7]</sup> Ennaifer *et al.* reported that IGT and DM are both frequently prevalent in cirrhosis. The study disclosed 68.8% of glucose metabolism disorder (GMD): 42.8% of DM and 26% of IGT, which is about four times more than in the Tunisian general population (9.9% vs. 42.8%), indicating that patients with cirrhosis are a high-risk population for GMD.

When A1c was correlated with ALD and CLD cases, it was significantly higher in CLD cases. In a similar study by Rao and Santhisree,<sup>[8]</sup> ALD group showed no significant increase in A1c when compared with control, but CLD group showed a significant increase, which may be due to endogenous IR which causes impaired IGT. CLD has a significant impact on hepatic glucose metabolism. Similar results have been reported by Ma *et al.*<sup>[9]</sup> It was observed that NAFLD patients had significantly higher A1c levels than control ( $P < 0.001$ ). The prevalence of NAFLD was significantly higher in subjects with increased A1c (A1c  $\geq 6.5\%$ ) than in those with normal range of A1c (51.71% vs. 25.20%;  $P < 0.001$ ). Bae *et al.*<sup>[10]</sup> observed HOMA-IR increased in the NAFLD patients as the level of A1c increased. The magnitude of association of

**Table 1: Etiology of acute liver disease and chronic liver disease cases**

	Hepatitis B	Hepatitis C	ATT induced	Alcoholic liver disease	NAFLD	Others	Total
ALD	18	7	8	0	0	7	40
CLD	16	15	0	18	11	4	64

ALD: Acute liver disease, CLD: Chronic liver disease, ATT: Antituberculous therapy, NAFLD: Nonalcoholic fatty liver disease

**Table 2: Comparison of parameters between acute liver disease and chronic liver disease patients**

	ALD (n=40)	CLD (n=64)	P
Age (years)	32.5±8.6	54.3±4.5	<0.0001
FPG (mg/dl)	91.8±5.4	115.7±17.9	<0.0001
PPG (mg/dl)	127.9±10.4	177±42.5	<0.0001
A1c	4.3±0.6	6.1±0.7	<0.0001

FPG: Fasting plasma glucose, PPG: Prandial plasma glucose, ALD: Acute liver disease, CLD: Chronic liver disease

**Table 3: Association of lipid profile acute liver disease and chronic liver disease cases**

	ALD	CLD	P
TG (mg/dl)	134.8±14.2	148.9±6.4	<0.0001
Cholesterol (mg/dl)	140±35.1	177.4±28.8	<0.0001
HDL (mg/dl)	50.4±5.1	44.4±6.1	<0.0001
LDL (mg/dl)	56.7±6.7	65.2±6.5	0.0001

ALD: Acute liver disease, CLD: Chronic liver disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride

HOMA-IR with A1c was greater in NAFLD patients than in non-NAFLD subjects ( $P < 0.001$  for interaction).

When the glycemic status was compared between chronic hepatitis B and C, it was found that mean FPG, PPG, and A1c were higher in HBsAg positive patients. The difference observed was insignificant. Huang *et al.*<sup>[11]</sup> showed that the prevalence of T2DM among HCV viremic subjects (18.0%, 86/478) was significantly higher than HBsAg positive subjects (11.4%, 155/1363,  $P = 0.001$ ) and those negative for both viral hepatitis markers (12.5%, 997/8004,  $P = 0.001$ ). HBV infection did not increase the association with T2DM. In a study conducted by Lecube *et al.*,<sup>[5]</sup> threefold increase in the prevalence of glucose abnormalities was observed in HCV positive patients with chronic hepatitis in comparison with HCV-negative patients (32 vs. 12%;  $P = 0.0003$ ). Among patients with cirrhosis, although both diabetes and IFG were more prevalent in anti-HCV positive patients (40%) than in anti-HCV-negative patients (36%), the differences were not statistically significant. Mansoor *et al.*<sup>[12]</sup> showed that the prevalence of diabetes in patients with CHC infection is higher than in the general population. Among patients of chronic hepatitis, it was seen that diabetes was more prevalent among anti-HCV-negative patients than among anti-HCV positive patients. In the group of patients with chronic hepatitis, both diabetes and IFG were more prevalent in anti-HCV-negative patients than in anti-HCV positive patients. Among patients with cirrhosis, diabetes was more prevalent in anti-HCV-negative patients. This is contradictory to studies mentioned above possibly due to small sample size. Allison *et al.*<sup>[13]</sup> noted that T2DM was five times more prevalent in HCV-related cirrhotic patients. Similar studies have shown the prevalence of T2DM in patients of cirrhosis.<sup>[14,15]</sup>

Lipid profile was compared between ALD and CLD; it was observed that the HDL levels were  $>40$  mg/dl in

86% of CLD cases. Forty-eight percent CLD cases had TG levels  $>150$  mg/dl. In 12% cases of CLD had cholesterol levels  $>200$  mg/dl. The mean TG, cholesterol, LDL levels were significantly higher and HDL levels significantly lower in CLD patients. Hannuksela *et al.*<sup>[16]</sup> found that alcoholic fatty liver and steatohepatitis (ASH) are characterized by elevated plasma TG, LDL levels are usually unaltered. HDL concentrations are reduced in acute ASH. In addition to hypertriglyceridemia, increased concentrations of serum total cholesterol and phospholipids have also been described. Targher *et al.*<sup>[17]</sup> showed that NAFLD displays a powerful atherogenic lipoprotein profile; serum TG, LDL, and Apo-B are increased, while HDL and LDL buoyancy are decreased. Liu *et al.*<sup>[18]</sup> found that acute hepatitis B is associated with transient hypertriglyceridemia. Chronic HBV infection is associated with reduced TG, total cholesterol, and HDL and with significantly increased serum adiponectin levels, but is not associated with IR and hepatic steatosis. McIntyre<sup>[19]</sup> found that liver cirrhosis is characterized by an abnormal plasma lipid and lipoprotein profile due to impaired liver biosynthetic capacity. Quantitative-qualitative lipid and lipoprotein derangements commonly include: (a) low serum levels of lipids and lipoproteins: cholesterol, TG, very-low-density lipoprotein (VLDL), HDL, Apo-AI, Apo-B, apoprotein-C (Apo-C), and Lp (a). Cicognani *et al.*<sup>[20]</sup> found a significant decrease in LDL, HDL, and total cholesterol serum levels compared with both chronic active hepatitis and control patients, while VLDL was only lower compared to controls.

When lipid profile was compared in CHC patients with diabetes and without diabetes, it was seen that the mean TG and cholesterol levels were significantly higher in patients with diabetes than those without diabetes. The results were similar to study by Bashir *et al.*<sup>[21]</sup> HCV with diabetes group showed a marked increase in serum cholesterol and TG levels.

## CONCLUSIONS

FPG, PPG, and A1c were significantly higher in patients of CLD when compared to ALD patients. When the glycemic status was compared between chronic hepatitis B and C, it was found that mean FPG, PPG, and A1c were higher in HBsAg-positive patients (insignificant) among patients of chronic hepatitis, it was seen that diabetes was more prevalent among anti-HCV-negative patients than among anti-HCV positive patients. In patients of cirrhosis, diabetes was diagnosed in 50% patients of CHC, and 61% patients without hepatitis C. TG, cholesterol, LDL levels were higher, and HDL levels were lower in CLD cases when compared to ALD (significant). In patients of CHC, those with diabetes had higher TG, cholesterol (significant) and LDL levels (insignificant). HDL levels were lower in cases with diabetes compared to patients without diabetes (insignificant). TG (significant), cholesterol (significant), LDL levels (insignificant) were higher, and HDL levels were lower (insignificant) in cases of CHC when compared to patients of chronic hepatitis B.

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## Conflicts of interest

There are no conflicts of interest.

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