

## Complications of Liver Cirrhosis in Patients with Hepatitis C Virus Infection and Type 2 *Diabetes mellitus*

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**Abstract:** This cross sectional observational study was conducted to evaluate the complications of liver cirrhosis in patients with Hepatitis C virus infection and type 2 *diabetes mellitus* and was conducted in medical ward of Liaquat University Hospital Hyderabad on patients having cirrhosis due to HCV. The structured proforma was filled in. Blood sample was collected for assessing HCV cirrhosis, liver failure, HBV infection to exclude from the study and blood sugar to confirm DM. Ultrasound of abdomen, ascitic fluid examination, upper GI endoscopy, liver biopsy, alpha-feto protein level, if required, were also done. A statistical package for social science (SPSS-13) was used to analyze the data. Out of 85 patients, 15(17.65%) were diabetics while 70(82.35%) were non-diabetics. Ascites in 60% of diabetics and 54.28% of non-diabetics; upper GI bleeding in 33.33% of diabetics and 22.85% of non-diabetics; hepatic encephalopathy in 26.66% of diabetics and 20% of non-diabetics; hepatocellular carcinoma in 13.33% of diabetics and 5.71% of non-diabetics were found. The presence of *diabetes mellitus* in hepatitis C virus liver cirrhosis increases the risk of ascites, encephalopathy and hepatocellular carcinoma.

**Key words:** Liver cirrhosis • HCV infection • Type 2 diabetes mellitus

### INTRODUCTION

There is evolving evidence that the presence of type 2 *diabetes mellitus* (DM) increases the prevalence and severity of various complications of liver cirrhosis due to hepatitis C virus (HCV) infection. Patients with chronic HCV infection have a significantly increased prevalence of type 2 DM as compared to controls [1-3]. There is direct experimental evidence for the contribution of HCV in the development of insulin resistance in humans, which finally leads to the development of type 2 DM [4]. Diabetes not only increases the prevalence of complications in HCV infected patients, but also increases the severity of complications and progression of chronic liver disease (CLD). Insulin resistance in HCV infected patients is related to grading of liver fibrosis and occurs already at an early stage in the course of HCV infection [5]. It is observed that in the absence of precipitating factors, the presence or severity of hepatic encephalopathy (HE) does not always show a strong and consistent relationship with the severity of liver disease or portal hypertension, suggesting that other

predisposing or precipitating factors may be involved [6], at least in patients with HCV cirrhosis and one of the factors is DM [7]. Diabetic cirrhotics with gastroesophageal varices (GOV) have a worse outcome in terms of failure to control bleed, rebleeding during hospital stay, multiple admissions with GOV bleed and the presence of anemia as compared to non-diabetic cirrhotics [8]. On the contrary, it is observed that autonomic neuropathy is common in patients with CLD and has been found to be an independent predictor of mortality in patients with cirrhosis, such patients are more prone to develop HE [9] and therefore autonomic neuropathy due to CLD, not due to DM increases the prevalence of HE. Keeping in view of such controversies, a local study was done to know the prevalence of complications of liver cirrhosis in patients with HCV infection and type 2 DM.

### MATERIALS AND METHODS

This cross sectional observational study was conducted at Department of Medicine, Liaquat University

Hospital Hyderabad during the period of six months from May 2007 to November 2007. This study was conducted on 85 adult patients of either sex. All were diagnosed cases of HCV cirrhosis due to hepatitis C virus. A total of 70 patients were non-diabetic and 15 were diabetic (type2). The inclusion criteria of the study was patients aged 18 years and above, of either sex having HCV cirrhosis while the exclusion criteria was patients with cirrhosis of liver other than HCV infection or having type 1 *diabetes mellitus* were not included in this study. The relevant referral patients from different units were also included in the study. A structured proforma was filled in, noting detailed history, general and systemic examination. Presence of HCV liver cirrhosis was confirmed by clinical examination followed by laboratory tests and imaging. Histopathological examination through liver biopsy was carried out in selected cases. All patients were also tested for DM and complications of HCV cirrhosis. The purpose and procedure of the study was explained to the patients or their attendants if patient is having altered conscious level. Informed consent was taken. In the history each patient was asked about distension of abdomen; any alteration in conscious level including poor concentration, confusion, increased irritability or muteness, tremors of hands or unconsciousness (in the past); hematemesis or/and melena at present or in the past; rapid loss of weight, abdominal pain with and without fever; bleeding from any site punctured or unpunctured and any medical procedure done in the past; history of *diabetes mellitus* with duration and whether multiple admissions in past; drug history especially diuretics. General and physical examination was done to note conscious level, presence of wasting of muscles, temperature, anemia, jaundice, leuconychia, spider telangiectasia, dupuyeteran contracture, bruises, gynaecomastia in males, menstrual disturbances in females, edema, flapping tremors, ascites, hepatomegally and splenomegally. Blood sample was collected for assessing HCV cirrhosis by detection of

Anti-HCV antibodies through ELISA method, liver failure, HBV infection to exclude from the study and blood sugar to confirm DM, biochemistry and hematological status. Ultrasound of abdomen to confirm cirrhosis of liver and to look for evidence of hepatocellular carcinoma, liver biopsy if ultrasound result is unequivocal for cirrhosis, as well as to confirm suspected hepatic nodule(s) for hepatocellular carcinoma, ascitic fluid tapping for DR and culture under ultrasound guidance if ascites is detected. X-ray of chest to look for hepatohydrothorax, upper GI endoscopy to check esophageal varices, alpha feto protein level, if required was done. A statistical package for social science (SPSS-13) was used to analyze data. Relevant descriptive statistics, frequency and percentage were computed for categorical variables like age groups, gender, marital status and complication, child's classification. Mean and standard deviation were computed for quantitative variables like age.

## RESULTS

A total of 85 patients of liver cirrhosis with hepatitis C virus infection (HCV) were included in this study. Of 85, sixty five (77%) patients were admitted / hospitalized whereas sixteen (18%) were visited out patient department while four (05%) were referred from Gynaecology outpatient department. The average age of the patients was  $48.5 \pm 8.4$  years (95% CI: 47.1 to 49.8). Most of the patients were 41-50 year of age (Fig. 1). Out of 85 patients, 50 (59%) were male and 35 (41%) were female with male to female ratio 1.43: 1. Majority of patients 60(71%) belonged to rural areas. Complications of liver cirrhosis with HCV infection are presented in Table 1. The most common complication was ascites that was observed in 47 (55.3%) patients in which 9 patients were diabetic and 38 were non-diabetic. Child-Pugh score of liver cirrhosis in patients with HCV infection is shown in Fig. 2.

Table 1: Complications of Liver Cirrhosis in Patients with HCV Infection According to Diabetes Status

Complication	Total <i>n</i> = 85	Diabetic <i>n</i> = 15	non Diabetic <i>n</i> = 70
Ascites	47(55.3%)	09 (60%)	38 (54.28%)
History of Upper GI Bleeding	21(24.7%)	5 (33.33%)	16 (22.85%)
History of Portosystemic shunt encephalopathy	18(21.17%)	04 (26.66%)	14 (20%)
Hepatocellular Carcinoma	06(7.05%)	02 (13.33%)	04 (5.71%)

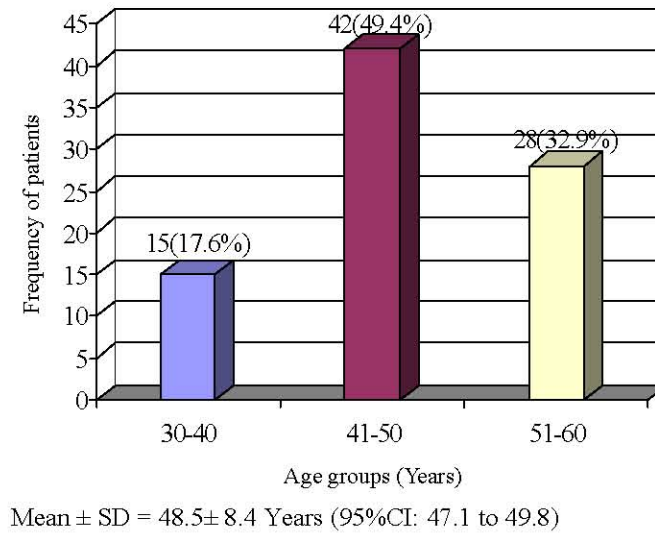


Fig. 1: Age Distribution of the Patients N=85

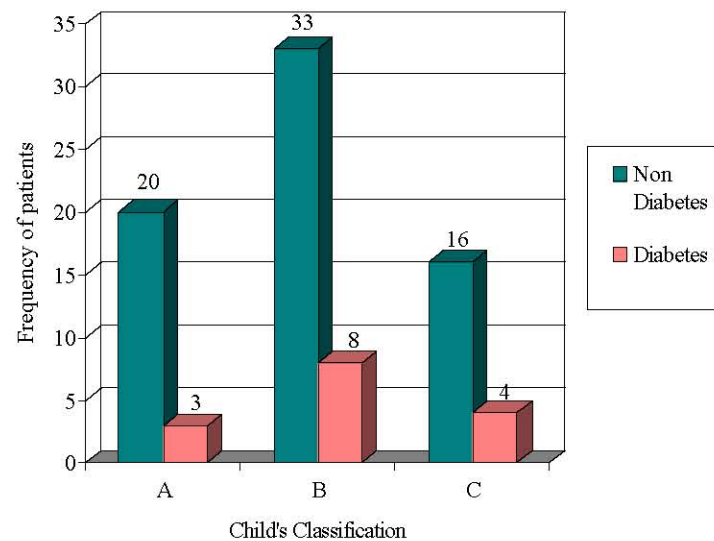


Fig. 2: Child's Classification of Liver Cirrhosis in Patients With Hcv Infection

## DISCUSSION

Many epidemiological studies have reported a higher prevalence of type 2 *diabetes mellitus* (DM) in subjects infected by HCV [10-12]. More recently various reports have described an increase in diabetes before the development of advanced liver cirrhosis [13]. Other factors, such as obesity, indicated by high (BMI); advanced age and family history of diabetes are associated with the higher incidence of diabetes in the HCV-infected population [13-15]. Emerging evidence in humans has shown that HCV infection induces hepatic steatosis and increases tumor

necrosis factor. It has been found that the presence of diabetes and hepatic steatosis may enhance fibrosis progression and hepatocellular carcinoma [16]. A high prevalence of diabetes has also been recently reported in patients with chronic hepatitis C virus (HCV) infection in the nontransplant population [17]. Many preliminary studies have shown that HCV infection may be an additional risk factor for the development of diabetes. To further explore, a study was conducted to determine the correlation of HCV infection and diabetes. The study design was a retrospective analysis on 1,117 patients with chronic viral hepatitis. They were analyzed for whether age, sex, race, HCV infection and cirrhosis were

independently associated with diabetes. The results showed that after the exclusion of patients with conditions predisposing to hyperglycemia, diabetes was observed in 21% of HCV-infected patients ( $P = .0004$ ). Multivariate analysis revealed that HCV infection ( $P = 0.02$ ) and age ( $P = .01$ ) were independent predictors of diabetes [18].

A recent study clearly demonstrated that hepatitis C is a precipitating factor for diabetes [19]. Another study was conducted to determine the prevalence of *diabetes mellitus* in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic liver disease. About 64 patients were having hepatitis C alone, 16 (25%) had diabetes. The distribution of hepatitis C virus genotype was similar in those with and without diabetes [19].

In present study, among 85 patients of HCV, about 15 (17.65%) were diabetic and 70 (82.35%) were non-diabetic. The percentage of diabetic patients among HCV positive persons is interestingly same in a study conducted in Islamabad, in which there were 411 patients with chronic hepatitis C and out of these, 71 (17.27 %) had diabetes mellitus [2]. The prevalence of diabetes mellitus in non-HCV population is found to be 5.6% only. In another study fifteen patients (33%) with HCV infection were found to have type 2 diabetes compared with 5.6% in the control group without liver disease ( $P < .001$ ) [20]. This showed strong association of HCV cirrhosis with *diabetes mellitus*.

In our study the most common complication was ascites that was observed in 47 (55.3%) patients in which 9 (60%) were diabetic and 38 (54.28%) were non-diabetic patients. This shows that ascites is more common in diabetic as compared to non-diabetic patients. Diabetes not only increases the frequency of ascites in HCV cirrhosis but also is one of the major causes of refractory ascites even in the absence of poor liver function. This was confirmed in a study in which almost 50% of the patients with refractory ascites had only slight impairment in liver function tests and were ascribed to Child-Pugh grade B because of tense ascites alone. The 'grade B group' differed from 'grade C group' by a greater frequency of hepatocellular carcinoma and diabetes. Thus, these factors may be important for the development of refractory ascites in patients with preserved liver function. Patients with diabetes had a shorter survival rate than without diabetes. Refractory ascites is associated with poor survival [21]. The hospitalized cirrhotic patients showed that diabetes is an independent predictive factor of death from liver failure [22].

History of upper GI bleeding was found in 21 (24.7%) patients in which 5 (33.33%) were diabetic and 16 (22.85%) were non-diabetic. Our results show that upper gastrointestinal bleeding is more common in diabetic as compared to the non-diabetic patients with HCV cirrhosis. Several factors, such as comorbidities (such as *diabetes mellitus*), clinical and endoscopic findings, were found to be related to rebleeding or death in patients admitted to the emergency room with UGI bleeding necessitating intensive care [23].

In our study the portosystemic shunt encephalopathy was observed in 18 (21.17%) patients in whom 4 (26.66%) were diabetic and 14 (20%) were non-diabetic. Hepatic encephalopathy is more common in diabetic as compared to non-diabetic patients. The presence or severity of HE does not always show a strong and consistent relationship with the severity of liver disease suggesting that other predisposing or precipitating factors may be involved. It has been suggested that DM may contribute to the presence and severity of HE in patients with HCV cirrhosis [5]. Ninety-five percent of diabetic patients with Child class B or C cirrhosis had severe hepatic encephalopathy in the study by Sigal *et al.* [7].

In our study hepatocellular carcinoma was found in 6 (7.05%) patients in which 2 (13.33%) were diabetic and 4 (5.71%) were non-diabetic. Again this dangerous complication of HCV cirrhosis is more frequent in diabetic patients, making diabetes a main culprit. Not only our study but an American study also coincided. In that American study 2061 HCC patients and 6183 non-cancer controls were recruited. The proportion of HCC patients with diabetes (43%) was significantly greater than non-cancer controls (19%) [24]. This means diabetes increase the risk of hepatocellular carcinoma 2.26 times. Our study showed 2.33 times greater risk of cancer in diabetic versus non-diabetic patients that is very much near to the finding in the American study. On the other hand, it was observed that patients suffering from chronic hepatitis C and DM had a 3-fold greater risk than non-diabetic patients with mild to moderate fibrosis of developing HCC in 5 years of follow-up (13% vs. 5%) [25,26].

Our results are very much near to the figure given for Child's Class B in a study done by Moreau *et al.*, in which there were 35 (47%) patients with Child-Pugh grade B. These patients differed from grade C patients by older age ( $60 \pm 9$  years vs.  $53 \pm 10$  years, respectively;  $P = 0.004$ ) and greater frequency of hepatocellular carcinoma (31% vs. 5%, respectively;  $P = 0.003$ ) and diabetes (46% vs. 15%, respectively;  $P = 0.004$ ). In a retrospective prospective

study 354 (98 with diabetes) of 382 eligible patients were followed during 6 years after inclusion into the study in which 110 were alive at the end of follow-up. Nishida *et al* [27] studied a group of 56 patients with cirrhosis and normal fasting blood glucose. After OGTT, 38% of the patients had DM. After 5 years of follow-up, compared with normal patients, those with diabetes had significantly higher mortality (5%, 44% respectively). By a multiple regression analysis, only serum albumin and DM were independent negative predictive factors of survival.

Future research should clarify the impact of diabetes in the natural history of HCV cirrhosis and the benefits of its early diagnosis and treatment for reduction of mortality. Future research should clarify if the treatment of diabetes may reduce the incidence and severity of complications of liver cirrhosis as well as the mechanisms by which diabetes increases morbidity and mortality of cirrhotic patient

In conclusion, in the light of our study it is recommended that treatment of hepatitis C should be started earlier so that progression to the development of cirrhosis of liver may be prevented/ delayed. As many studies now confirm the strong association of hepatitis C virus infection with type 2 *diabetes mellitus*, therefore early treatment of hepatitis C infection may also prevent/ delay the development of *diabetes mellitus*. Further it is recommended that regular screening of HCV infected patients for diabetes should be done. If cirrhosis has developed and diabetes is also diagnosed in the same patient then treatment of diabetes should be instituted to prevent the severity of complications of HCV cirrhosis. However certain limitations should be considered while starting treatment of diabetes.

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