

Research Article

Diabetes Mellitus Among Patients with Cirrhosis Due to Hepatitis C Virus and its Association with Hepatic Encephalopathy

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Abstract

Background: Diabetes Mellitus (DM) is frequent in chronic liver disease and there is an increased association of DM with Hepatitis C and hepatic encephalopathy (HE). In our setup such studies are not published and we do not have the updated knowledge of the above mentioned phenomena.

Objectives: To determine the frequency of DM in HCV cirrhotic patients and association of HE in HCV Cirrhotic patients with DM

Materials And Methods: This Analytical cross-sectional study was conducted in Medicine Department, Mayo hospital, Lahore. 100 patients with HCV associated cirrhosis were included using non-probability purposive sampling. Patients were stratified as diabetic and non-diabetic according to ADA criteria and presence of HE was determined clinically. Frequency and percentage of HE & diabetes were calculated and odds ratio was calculated to determine association. P-value <0.05 was considered significant.

Results: The mean age of patients was 44.43±10.16 years and there were 66% males and 34% females. 34% among HCV cirrhosis patients were diabetic. HE was seen in 31(91.2%) of the diabetic patients and in 48(72.7%) of non-diabetic patients with odds ratio of 3.875 (p-value 0.016)

Conclusion: There is a significant association between diabetes mellitus and HE among patients with HCV associated cirrhosis.

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Introduction

Hepatic Encephalopathy (HE), an intermittent or permanent syndrome of neurological dysfunction, is potentially reversible. The clinical spectrum has a wide variation from asymptomatic to comatose. Among the asymptomatic patients,

abnormal psychometric tests are the only detectable abnormality.¹ A few signs of HE may be seen in about 70% of cirrhotic patients on careful examination while the overt features of HE including coma are observable in up to 30% patients who die of end-stage liver disease.^{2,3} Ali et al reported that 3.5% of Pakistani population is infected with Hepatitis C

virus; the overall result being the epidemic proportion of cirrhosis in Pakistan.⁴ Genotypes 1a, 2a & 2b were found in 10.89%, 13.22% & 6.61% cases, respectively. About 6.1% cases had mixed genotypes.⁵ HE, a major neuropsychiatric complication, indicates poor prognosis amongst cirrhotic patients.^{6,7}

Various pathological factors may result in HE and one of the major pathways is increased ammonia production by gut bacteria.^{8,9} Autonomic dysfunction (AD) of the gastrointestinal tract leads to altered gut motility, which in turn enhances the duration of exposure to intestinal flora. AD and smooth muscle dysfunction leading to gastroparesis and motility disorders are frequently observed among cirrhotic patients and may represent an additional mechanism underlying development of HE.^{10,11}

Diabetes Mellitus is commonly seen in patients with chronic liver disease. HE was present in 50.3% of patients. In all, 118 patients had DM (33.5%). Patients with DM had a significantly higher prevalence (58.5% vs 42.6%; $P = 0.03$) and severity of HE ($P = 0.01$) than patients without DM.¹² Nearly 50% diabetic patients have delayed gastric emptying, delayed duodenal transit and sluggish intestinal motility resulting in bacterial over growth.¹³ Due to shared pathophysiological mechanism of altered GI motility in diabetes and cirrhosis, it is anticipated that patients having both cirrhosis and diabetes have higher likelihood of HE. Frequency of Hepatic Encephalopathy in HCV cirrhotic patients is 95% in Diabetic and 78% in Non-Diabetic patients.¹⁴ Improved glycemic control in these patients will ameliorate any reversible effect of autonomic dysfunction and this meticulous control of Diabetes in Cirrhotic patients will have positive effect on overall survival of the patients.¹⁵

HCV-associated cirrhosis is frequently seen in Pakistan. The prevalence has been reported to be 6.2%.¹⁶ HE is a common complication leading to frequent hospital admission. However, the association of diabetes and its complication with the development of HE has not been studied in our population. This study was planned to reveal this important and relevant association with the objectives of determining the frequency of diabetes in HCV cirrhotic patients and discovering the association of encephalopathy in HCV cirrhotic patients with

Diabetes Mellitus.

Methods

Study Design and settings

This Analytical cross-sectional study was conducted in the Department of Medicine, Mayo Hospital Lahore, a leading public sector tertiary care teaching hospital in Pakistan.

Sample size and Lab work

Sample size of 100 patients was calculated with 95% confidence level, 9.5% margin of error and taking expected percentage of diabetes i.e. 33.5 in patients of HCV liver cirrhosis. Non-Probability purposive sampling technique was used to select either gender patients with HCV cirrhosis and ages ranging from 16 to 60 years. Cirrhosis was confirmed with Ultrasonography abdomen and Hepatitis C was confirmed with ELISA. Patients with active gastrointestinal bleeding (hematemesis and melena), active infections like urinary tract infection, respiratory tract infection or increase white blood cells count ($>11000/\text{mm}^3$), renal failure and history of taking sedatives/hypnotics like benzodiazepine, methadone, narcotics were excluded. American diabetes association criteria was used to diagnose DM i.e., patients were considered diabetic if they were being treated for DM (oral hypoglycemic agents or insulin) or had fasting blood sugar level above 126 mg/dl and/or post-prandial blood sugar level > 200 mg/dL. HE was diagnosed clinically on presence of any of the symptoms/signs of altered sleep patterns, concentration disorders, irritability, asterixis associated with impaired number connection test (NCT), a validated neuropsychometric test for diagnosis of HE. Test was considered impaired if the time taken by the patient is more than 30 seconds.

Data Collection

After taking informed consent, patient's demographic profile including name, age, sex, address was noted. Detailed history and examination was done and presence/absence of HE was determined. The patients were classified as diabetic and non-diabetic (on the basis of above mentioned criteria).

Statistical Analysis

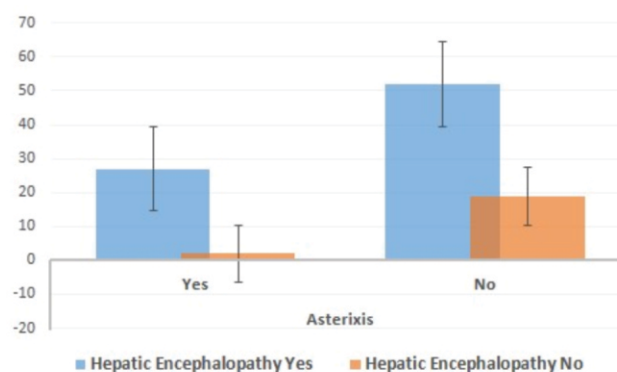
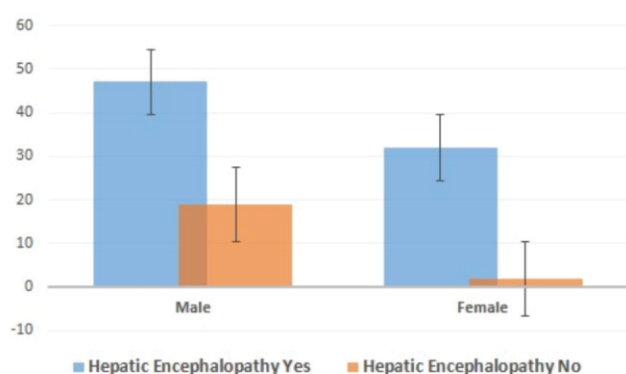
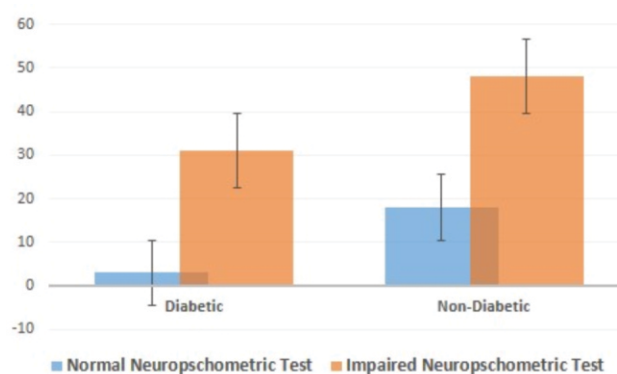
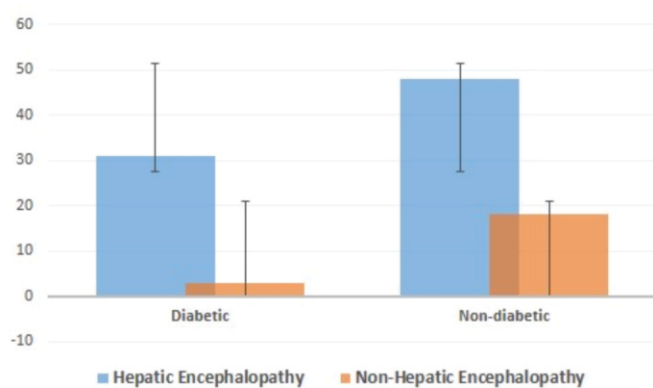


Fig I: Graphic Representation of Diabetes and Hepatic Encephalopathy in the Sampled Population

SPSS version 26.0 was used for data analysis. The quantitative variables like age was presented as mean \pm S.D. The qualitative variables like gender, diabetic and non-diabetic, and the Hepatic Encephalopathy in diabetic and non-diabetic group were calculated as frequency and percentages. The qualitative data was compared by Chi-Square test and odds ratio (OR) was calculated as a measure of association between HE and diabetes considering $OR > 1$ as positive association. P-value 0.05 was taken as significant for all the analyses conducted.

Results

The mean age of patients was 44.43 ± 10.16 years. There were 66 (66%) males and 34 (34%) females. In this study the frequency of diabetes was determined as 34% among HCV cirrhosis patients (Fig I).

Among diabetic patients the frequency of Insomnia was 24 (64.7%) while in non-diabetic patients the frequency of insomnia was 43 (65.2%). Day night reversal was present 23 (67.6%) diabetic patients while 35 (53%) in non-diabetic patients. Irritability was seen in 26 of the diabetic and 40 of the non-diabetic patients. Among diabetic group, 19 (55.9%) patients had asterixis while in non-diabetic group 10

(15.2%) have Asterixis. Moreover, 31 (91.2%) diabetic patients had abnormal neuropsychometric test while 48 (72.7%) non-diabetic patients had abnormal neuropsychometric test (Table I).

Hepatic Encephalopathy was found significantly higher in the diabetic patients as compared to non-diabetic patients. 91.2% of the diabetic patients were positive for Encephalopathy (Fig I). While Encephalopathy was higher in males as compared to females.

Binary Logistic Regression was conducted to assess the strength of association between Diabetes in

Table 1: Table I: Description of different Parameters in Diabetic Versus Non-Diabetic Patients Regarding Hepatic Encephalopathy

Variables	Diabetics (n=34)	Non-diabetics (n=66)	p-value
Insomnia	22 (64.7%)	43 (65.2%)	0.4823
Day Night Reversal	23 (67.6%)	35 (53%)	0.1457
Poor Concentration	26 (76.5%)	55 (83.3%)	0.2036
Irritability	26 (76.5%)	40 (60.6%)	0.0563
Asterixis	19 (55.9%)	10 (15.2%)	0.0000
Normal Neuropsychometric Test	3 (8.8%)	18 (27.3%)	0.0160
Hepatic Encephalopathy	31 (91.2%)	48 (72.7%)	0.0160

Cirrhotic Patients with Hepatic Encephalopathy. It was used to predict the odds of being diabetic versus different variables (Table II). Statistically poor concentration (Yes) was found significantly associated as risk (Odds= 9.3; P-value=0.03) for diabetes. Day night reversal (Yes) was recorded as a risk for being diabetic; found as a significantly (Odds=0.1; C.I= 0.32-0.37; P-value=0.032). Other factors found as risk factors for diabetes included Asterixis and Hepatic Encephalopathy. Hepatic Encephalopathy was found strongly associated (Odds= 4.15; C.I= 1.5-14.2; P-value= 0.04) as risk with diabetes.

Table 2: Binary Logistic Regression of to Assess the Odds of Occurrence of Diabetes Versus Studied Independent Variables

Variables	S.E	Wald	Odds Ratio	95% C.I	P - Value
Gender	.522	.882	.612	.220-1.70	.348
Insomnia	.698	2.357	.343	.087-1.34	.125
Day night Reversal	.812	4.616	.175	.036-0.85	.032
Poor Concentration	1.075	4.306	9.304	1.132-76.4	.038
Irritability	.594	.055	1.149	.359-3.67	.815
Asterixis	.624	12.517	.110	.032-0.37	.000
Neuropsychometric Test	.765	.681	1.880	.420-8.42	.409
Hepatic Encephalopathy	.665	4.15	3.87	1.05-14.26	0.04

Binary Logistic Regression
Wald Statistics: Variable(s) entered on step 1: Gender, Insomnia, Dnr, P.Conc, Irritability, Asterixis, NT.

Discussion

Hepatic Encephalopathy is a serious complication of cirrhosis and is the underlying mechanism of death in 30% of cirrhotic patients. The neuropsychiatric aberrancy of HE may be chronic due to underlying portal-systemic shunting or may have an acute precipitating factor. Early identification of precipitating factors and comorbidities is the key to the diagnosis and treatment of this critical condition.^{17,18}

In Pakistan, cirrhosis is being reported in epidemic proportions in close conjunction with the high prevalence of hepatitis B and C.¹⁹⁻²¹ The presence of certain co-morbid conditions especially diabetes mellitus have been reported to enhance the risk of HE among cirrhotic patients.²² The purpose of this study was to establish the frequency of HE among HCV infected cirrhotic patients with and without Diabetes Mellitus. In this study, the average age of patients was 44.43±10.16 years. In this study the frequency of diabetes was determined as 34% among HCV cirrhosis patients while in 66% patients the diabetes was not seen. In our study, the odds ratio was calculated as 3.875 (95% CI; 1.053, 14.26) which showed that HCV diabetic cases has almost four time

more chance of developing hepatic encephalopathy as compared to those HCV cases who do not have diabetes. The exact underlying mechanisms are still undefined but diabetic autonomic neuropathy & consequent constipation along with impaired ammonia metabolism may underlie the phenomenon.²³ DM also increases the risk of development of hepatocellular carcinoma (HCC) among cirrhotic patients.²⁴ Both DM and HCC have share common associated factors, but association between them is poorly identified. Numerous surveys have demonstrated a significant association between DM pathogenesis and prognostic features causing high HCC prevalence. Consequently signifying DM as a significant risk factor for the development of HCC.²⁵ According to our findings HE was seen in 31(91.2%) of the diabetic patients and in 48(72.7%) of non-diabetic patients. The odds ratio was calculated as 3.875 (95% CI; 1.053, 14.26) which showed that HCV diabetic cases has almost four time more chance of developing hepatic encephalopathy as compared to those HCV cases who do not have diabetes. The difference between both groups was significant i.e. p-value= 0.0160. In our series for HE the patients were diagnosed clinically on presence of any of the features of sleep disturbance including insomnia & reversal of day/ night, behavior & mood changes, impaired concentration, or asterixis associated with impaired neuro-psychometric test (NCT). Test was considered impaired if the time taken by the patient exceeds 30 seconds. Among diabetic patients the frequency of Insomnia was 24 (64.7%) while in non-diabetic patients the frequency of insomnia was 43(65.2%). Day night reversal was present 23 (67.6%) diabetic patients while 35(53%) in non-diabetic patients. Irritability was seen in 26 of the diabetic and 40 of the non-diabetic patients. Among diabetic group, 19 (55.9%) patients had asterixis while in non-diabetic group 10 (15.2%) had asterixis. Moreover, 31(91.2%) diabetic patients had abnormal neuropsychometric test while 48 (72.7%) non-diabetic patients had abnormal neuropsychometric test. The significance of optimal glycemic control among cirrhotic patients cannot be underrated as it is a potential contributory factor to development of HE. Binary Logistic Regression analysis was conducted to assess the association of different factors with diabetes and hepatic Encephalopathy. Factors having p value greater than 0.25 were retained and assessed through binary logistic regression at a significance level of 95%. Different factors were found significantly associated with diabetes including day night reversal, asterixis and hepatic encephalopathy. The results of the current study were in line with the

previous study conducted in china.²⁴

Conclusion

Hepatic encephalopathy (HE) is significantly associated with diabetes mellitus. Now HCV patients should be screened for glycemic level and diabetes to prevent development of hepatic encephalopathy.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest

Funding Source: None

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