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SHORT ARTICLE

Correlation of presence and severity of glucose derangements with severity of Liver Cirrhosis: a hospital-based cross sectional observational study from New Delhi

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Abstract

Background Association between liver cirrhosis (LC) and glucose intolerance has been known since long. Many studies in the past have attempted to explore the correlation of glucose metabolism disorders (GMD) with the severity of LC with mixed results (some favouring i.e. higher prevalence of GMD in more severe LC; others negating). This study was conducted to shed further light on the significance of this association.

Objective This study has been carried out with the aim of studying the correlation between GMD and the severity of LC, as determined by the Child-Turcotte-Pughe (CTP) score.

Methods 100 patients with LC admitted in medical wards were studied and tested with fasting plasma glucose (FPG), 2 h post-75 g oral glucose load plasma glucose (PPG), glycosylated haemoglobin (HbA1c) and fasting plasma insulin. They were categorized based on the severity of LC into CTP A, B or C class and then patients belonging to different classes were compared for the presence of GMD and insulin resistance (IR).

Conclusion Out of 100 patients, 6, 21 and 73 were respectively found as falling under CTP class A, B and C of LC. The frequency of diabetes mellitus (DM) was found to progressively increase with worsening grade of cirrhosis (17%-A, 24%-B and 27%-C), however this was not significant (p value 0.82). The p values for IR, GMD (pre-diabetes or DM), pre-diabetes (pre-DM) were 0.629, 0.382 and 0.189 respectively. To conclude, development of GMD and IR may be independent of the severity of LC. However more studies may be required to further study this association.

Keywords Liver cirrhosis · Glucose metabolism disorders · Severity · Diabetes mellitus · Insulin resistance

Introduction

Association between liver cirrhosis (LC) and glucose intolerance has been known since long. This association includes not only patients of LC developing glucose metabolism disorders (GMD) but also known diabetics developing liver disease progressing to cirrhosis. GMD refer to a spectrum of abnormalities in glucose tolerance. These include asymptomatic pre-diabetes mellitus (Pre-DM) which can be present either in the form of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) as well as overt diabetes mellitus (DM).

Cirrhosis is characterized by an increased burden of inflammation. On the other hand, conditions that are characterized by GMD or insulin resistance (IR), such as DM, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and pregnancy are also associated with high inflammatory burden. Thus, a link between cirrhosis and impaired glucose metabolism could exist via the inflammatory pathway.

Evidence implicating systemic inflammation in the pathogenesis of cirrhosis is compelling. Easily measured serum markers (procalcitonin, CRP: lymphocyte count ratio, SIRS) and certain clinical parameters (total leucocyte count, mean platelet volume, neutrophil: lymphocyte ratio) have been studied as prognostic tools in cirrhosis for follow-up, monitoring and management.

Hyperglycaemia in DM per se leading to progression of liver disease to fibrosis in NAFLD was found to be related to overexpression of connective tissue growth factor (CTGF), which then likely induces the transcription of several ECM

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Table 1 The WHO Criteria For Diagnosing DM/ IFG/ IGT

Condition	Fasting plasma glucose	2 h-post 75 g oral glucose load plasma glucose	HbA1c	
Unit	mmol/L (mg/dL)	mmol/L (mg/dL)	mmol/mol	%
Normal	< 6.1 (< 110)	< 7.8 (< 140)	< 42	< 6.0
IFG	≥ 6.1 (≥ 110) & < 7.0 (< 126)	< 7.8 (< 140)	42–46	6.0–6.4
IGT	< 7.0 (< 126)	≥ 7.8 (≥ 140) but < 11.1 (< 200)	42–46	6.0–6.4
DM	≥ 7.0 (≥ 126)	≥ 11.1 (≥ 200) and/or,	≥ 48	≥ 6.5

(extracellular matrix components) components. Also insulin brings about induction of CTGF in hepatic stellate cells (HSC); IR and reactive hyperinsulinaemia being present in all cirrhosis patients irrespective of aetiology. Many pro-inflammatory cytokines are up regulated whereas the anti-inflammatory ones are decreased.

World over, in many studies analysing this association, the prevalence of GMD as well as IR was found to be associated closely with the Child-Turcotte-Pughe score (CTP score), with increasing prevalence with worsening grade of LC. Certain others found no association between the two. Hence, this study was planned to examine this further.

Materials and methods

A hospital-based cross-sectional observational study was conducted in the department of General Medicine, Lady Hardinge Medical College & Sucheta Kriplani Hospital, New Delhi from November 2015 to April 2017 wherein 100 adult in-patients with LC were enrolled after taking a written informed consent.

Sample size was calculated using the formula :

$$n = (1.96)^2 pq/E^2 \text{ at } 95\% \text{ confidence level}$$

Considering the fact that the prevalence of GMD in hospitalized cases of LC was reported by various studies between 33–96% [1–4] and also presuming the estimated prevalence as 70%, at 95% level of significance with an allowable error of 15% (of 70%) the calculation of statistically valid sample size was done as follows: p was the probability of GMD in patients of LC (0.7), q was the complement of p i.e. 1-p (0.3) which reflected liver cirrhosis free of GMD.

$$n = 1.96^{*}1.96^{*}0.7^{*}0.3/\left(15/100^{*}0.7\right)^2$$
$$= 73.17 \text{ or } 74$$

Applying a 10% drop out/ non response to this (which included loss to follow-up due to leave against medical advice/ absconding), sample size should have been 81.4 or 82. A final sample size of 100 was taken in view of availability of cases and better credibility.

LC was diagnosed by a combination of clinical/ biochemical/ radiological findings: patients with clinical signs of liver cell failure or clinical features of portal hypertension with hypoalbuminemia, reversal of albumin and globulin ratio (A:G ratio), deranged prothrombin time (PT) and international normalized ratio (INR); ultrasound abdomen showing surface nodularity, coarse/altered echo texture, parenchymal inhomogeneity in the liver without or with ascites alone or with features of portal hypertension like portal vein diameter ≥ 13 mm, presence of collaterals and splenomegaly. Patients who were suffering from hepatocellular carcinoma, acute/ chronic pancreatitis/ pancreatic cancer or endocrinopathies (such as Cushing's syndrome, acromegaly, glucaganoma, pheochromocytoma, polycystic ovarian syndrome) or who had undergone pancreatectomy were excluded. Also excluded were those on corticosteroids or those who had received it within the last 48 h.

- History, clinical examination and investigations were recorded as per a pre-defined proforma. All the study patients were subjected to fasting plasma glucose (FPG) and fasting plasma insulin and 2 hours-post 75 grams oral glucose load plasma glucose (PPG). Glucose metabolism disorders were diagnosed if the patient was a known DM/ Pre-DM (IGT/ IFG) or was detected to have DM/ Pre-DM after entering the study. The criteria (WHO [5]) that were used for diagnosing DM, IGT and IFG are as follows: (Table 1)

Those with symptoms suggestive of DM and one abnormal fasting or post prandial value were labelled as having GMD. In case of an asymptomatic patient, one abnormal value was followed by a repeat next day testing. Patients were labelled as GMD only if both reports were abnormal. IR was calculated using the homeostatic model assessment-insulin resistance formula (HOMA-IR) which is given below:

Table 2 Criteria For CTP Scoring

SCORE	1	2	3
Serum bilirubin (mg/dl)	< 2.0	2.0–3.0	> 3.0
Serum albumin (g/dl)	> 3.5	3.0–3.5	< 3.0
Prothrombin time (seconds prolonged)	0–4	4–6	> 6
Ascites	None	Easily controlled	Poorly controlled
Hepatic encephalopathy	None	Minimal	Advanced

- For patients found to be having GMD, appropriate treatment required for controlling plasma glucose was provided and noted.

Biochemical methods used for various estimations: Blood glucose by glucose oxidase peroxidase method, glycosylated haemoglobin by latex agglutination method (NGSP certified)using the D-10 instrument, fasting plasma insulin by electro chemiluminescence immunoassay, PT-INR-apTT by ACL elite pro machine, serum bilirubin by modified Jendrassik's method, albumin by dye- (bromcresol green) binding method.

$$\text{HOMA} - \text{IR} = \text{FPG (mg/dL)}^{*}\text{Fasting Plasma Insulin (microU/mL)}/405$$

A HOMA-IR cut off of 2.5 was taken (Singh Y et al. [6]) for diagnosing insulin resistance.

- The severity of liver disease was assessed using the CTP score. [7] (Table 2)

The CTP score was calculated by adding the scores of the five factors (range from 5 to 15). Child Pugh class can be A, B or C. Decompensation indicates cirrhosis with a Child–Pugh score ≥ 7 (class B). This level has been the accepted criterion for listing for liver transplantation.

Class A CTP: scores 5 and 6
Class B CTP: scores 7 to 9
Class C CTP: scores 10 or more

Patients belonging to different classes were compared for the presence of GMD.

- All in-patients of LC had their blood sugar testing at least twice once at admission and again prior to discharge to check for the presence of stress induced hyperglycaemia.

Statistical analysis

Categorical variables were presented in number and percentage (%). Qualitative variables were correlated using Chi-Square test/ Fisher's exact test. A p value of < 0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Out of 100 patients, 6, 21 and 73 were respectively categorized as CTP grade A, B and C of LC. The frequency of DM was found to progressively increase with worsening grade of cirrhosis (17%, 24% and 27%, respectively for CTP Grade A, B and C), but the increase was not significant (p value = 0.82). Likewise, association of severity of liver cirrhosis was not significant with GMD or Pre DM (Table 3).

Likewise, no significant association between increasing severity of LC and IR was found; *p* value = 0.629 (Table 4).

Out of the 100 patients studied, 26 were found to have DM (15 were newly diagnosed, while 11 were previously diagnosed cases).

Table 3 GMD And Severity Of Liver Cirrhosis

Severity of LC	Total	GMD			
		No	Yes	Pre DM	DM
A	6	5 (83.33%)	1 (16.67%)	0 (0.00%)	1 (16.67%)
B	21	11 (52.38%)	10 (47.62%)	5 (23.81%)	5 (23.81%)
C	73	45 (61.64%)	28 (38.36%)	8 (10.96%)	20 (27.40%)
Total	100	61 (61.00%)	39 (39.00%)	13 (13.00%)	26 (26.00%)
p value	-		0.382	0.189	0.82

$\chi 2 = 1.926$, df = 2

Table 4 IR And Severity Of LC

Severity of LC	Total	IR	
		No	Yes
A	6	5 (83.33%)	1 (16.67%)
B	21	14 (66.67%)	7 (33.33%)
C	73	55 (75.34%)	18 (24.66%)
Total	100	74 (74.00%)	26 (26.00%)

$\chi 2 = 0.927$, df = 2, p value = 0.629

Discussion

In the present study, increasing trend in DM was observed with increasing severity of cirrhosis (approximately 17%, 24% and 27% in CTP Grade A, B and C, respectively), but it did not reach statistical significance. Hence, no significant increase in the frequency of GMD (both pre-diabetes and DM) could be demonstrated with worsening grade of liver disease. However, in the review of available literature, a majority of studies [8–14] were found favouring a positive correlation between the severity of liver disease and the occurrence of GMD, i.e. more severe the liver disease, a greater proportion of subjects were found to have GMD. Caronia S et al. [8] demonstrated the percentages of the population with cirrhosis due to HCV found to have DM as approximately 10%, 22% and 32%, respectively for Child Pugh A, B, C; similarly, for cirrhosis due to HBV the statistics were 4.5, 8.9 and 12.8%, respectively. In a study of 121 cirrhotic patients from central India (Vasepalli P et al. [15]), the presence of hepatogenous diabetes was found to be well associated with the severity of cirrhosis in the form of higher MELD score (> 15) and CTP score (> 10). In yet another 2017 study [16] of 100 patients with CLD from Kolkata, significant association between impaired glucose tolerance and diabetes mellitus with the severity of CLD (based on CTP score) was found (p value < 0.05).

Only a few studies (Mukherjee S et al. [17], Muller MJ et al. [18]) had findings similar to the present study. Also in a study done at Mayo Clinic Rochester between Jan 2006 and Dec 2011 (Yang JD et al. [19]), one of the findings was that the severity of hepatic decompensation determined by the mean CTP and the MELD scores was lower in patients with diabetes mellitus as compared to those without it.

In the present study, no significant association between increasing severity of LC and IR was found in the present study. Few studies support this finding, [18, 20] whereas others [21–23] suggest that prevalence of IR increases with increasing severity of liver disease. In a study [24] published in 2020, IR was observed in 20 (74%) cirrhotic patients and CTP C patients had higher HOMA-IR than those with Child class B cirrhosis; however, this difference was statistically insignificant (p = 0.07). In yet another study done in Amritsar [25] on 100 non-diabetic patients with cirrhosis, a significant increase in IR was noted in patients with increased CTP score and advanced disease.

Many studies from reviewed literature were found to have explored and found inflammation to be a significant factor associated with chronic liver disease including cirrhosis. For instance, in a retrospective study [26] done comparing patients of chronic hepatitis C with healthy controls and also patients of chronic hepatitis C with or without significant fibrosis, a significant positive correlation was found between CRP to lymphocyte count ratio (an inflammatory marker) and APRI score (a non-invasive index of fibrosis).

Likewise, other conditions characterized by IR and GMD also have high inflammatory burden. Human studies of neuregulin-4 (which is believed to have anti-atherogenic and anti-inflammatory properties) have suggested its association with insulin resistance, impaired glucose metabolism, obesity, NAFLD, DM and metabolic syndrome. In a study [27] to observe the relationship of neuregulin-4 and control of diabetes, neuregulin-4 was found to be significantly increased (as a part of physiologic protective overexpression) in patients with poorly controlled DM vis-ă-vis well controlled DM and controls. Association between low-grade inflammation related to obesity and metabolic syndrome with its attendant complications has been well studied. In another study [28] conducted to assess mean platelet volume as an inflammatory marker in well and poorly controlled DM, it was found to positively and strongly correlate with both HbA1c & FPG. Uric acid is known to be an inducer of insulin resistance and a sensitive marker of underlying inflammation. A proposed novel marker-uric acid to HDL cholesterol ratio (UHR) was found to be significantly lower in well controlled DM as compared to poorly controlled DM in a study. [29] Furthermore, sensitivity and specificity of UHR in predicting metabolic syndrome were found to be better than most of the sensitivities and specificities of the five criteria of metabolic syndrome. UHR was also significantly higher in NAFLD compared to healthy controls; it was suggested that elevated UHR levels should be considered a useful tool in diagnosing hepatic steatosis [30].

Conclusion

Though a rising trend was demonstrated in the frequency of GMD with higher grade of cirrhosis, this association did not reach a significant level. More studies with a larger sample size might help in checking this further. However for now, we conclude that the development of GMD and IR may be independent of the severity of LC. Nevertheless, we suggest that presence of GMD and IR should be screened in all cirrhosis patients irrespective of the severity class.

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Declarations

Ethical approval This study was approved by institutional ethical committee.

Conflict of interest The authors have no relevant financial or non-financial interests that are directly or indirectly related to this work to disclose.

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