Outcome of Patients with Liver Cirrhosis and Type 2-Diabetes

Gamal A. Eltohamy[1] and Hassan E. EI-Batae[2]

[1]Department of Internal Medicine, AI-Azhar University, Egypt.
[2]Department of Tropical Medicine, Tanta University, Egypt.
gamaltohamy@ymail.com

Abstract: Type 2-DM may affect the mortality and outcome of cirrhotic patients. However, few studies assessing the prevalence and the impact of type 2-DM on the outcome of cirrhotic patients are available. The present study was performed to evaluate the rate of type 2- DM and their impacts on the outcome of patients are available with liver cirrhosis. The study included 138 patients with liver cirrhosis, with and without diabetes at AI-Azhar and Tanta University Hospitals between January 2009 and October 2010. Patients were divided into two groups; group I included 76 patients with type 2-diabetes; group 11 included 62 patients without diabetes. History and clinical examination were performed to all patients with special emphasis on diabetes: Child's Pugh Score, and complications of liver cirrhosis. Liver and renal function tests, FBS, PPBS, HbAlc, a-feto protein, CBC, viral markers and abdominal ultrasongraphy were performed to all patients. The incidence of type 2-diabetes (group I) was 76/138 (55%) most of them had HCV infection (56/76 =73.5%) and 20% had ~V infection; in contrast to non-diabetic patients had IiBV infection 31/62(50%) and 27/62 (43.5%) had HCV infection. Group I patients had severe liver disease (Child Pugh score C) than group 11 (p<0.001). Serum levels of hemoglobin, platelet and albumin were significantly lower while serum levels of bilirubin, ALT, AST, FBS, PPBS, creatinine, HbAlc, a-feto protein, BM! and HOMA IR were significantly higher in group I. All liver cirrhosis complications were significantly higher in group I. Using Multiple regression analysis the following variables were predictors of death in patients with liver cirrhosis; high serum levels of HbAlc (OR=4.5, 95% CI=2.5-9.5, r=0.680, p<0.01), Child-Pugh class C (OR=4.5, 95% CI=2.2-8.5, r=0.620, p <0.01), low serum levels of albumin (OR=3.8, 95% CI=1.3-5.7, r=0.580, p <0.01) and high serum levels of creatinine (OR=3.2, 95% CI=1.1-3.2, r=0.500, p <0.01).Conclusions: The incidence of DM was significantly higher in cirrhotic patients (55%) and significantly increases their complications and mortality rate. High HbAlc, Child-Pugh class C, low serum levels of albumin and high serum levels of creatinine were impendent predictors of death.

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1. Introduction

The association between liver disease and diabetes mellitus (DM) is well known. Overt DM was observed in 30 to 40% of patients with liver cirrhosis (Omar *et al.,* 2011). However, impaired glucose tolerance and sub clinical DM have been identified by oral glucose tolerance test in about 38 and 25% of cases, respectively (Tolman *et al.,* 2007). Type 2-diabetes increases the prevalence and severity of various complications of liver cirrhosis due to hepatitis. Also, patients with chronic HCV infection have a significantly increased prevalence of type 2 diabetes as compared to controls (Knobler and Schattner, 2005). 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 (Petit *et al.,* 2001).

More recently, new insights into this association came from the recognition that: (a) DM itself may be a cause of liver disease, via non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), cirrhosis, and ultimately hepatocellular carcinoma; (b) hepatitis C virus may have direct diabetogenic effects; and (c) post-transplantation DM is a major 'cause of morbidity and mortality in subjects following liver transplantation (Memon *et al.,* 2011).

The present study was performed to study the rate of type 2- DM and its impact on the outcome of patients with liver cirrhosis.

2. Patients and Methods

The study included 138 patients with liver cirrhosis, with and without diabetes at AI-Azhar and Tanta University Hospitals between January 2009 and October 2010. Patients were divided into two groups; group I included 76 patients with type 2-diabetes; group 11 included 62 patients without diabetes.

Diagnosis of cirrhosis was based on clinical, biochemical, ultrasound characteristics of altered

echo texture, shrunken liver and irregular. margins and liver biopsy in suspected cases. Diagnosis of diabetes was made in agreement with American Diabetes Association criteria (2003).

History and clinical examination were performed to all patients with special emphasis to Child's Pugh Score, an< complications of liver cirrhosis all(diabetes. Liver and renal function tests FBS, PPBS, CBC, HbA1c, HbA1c, vira: markers (HBS-A:g-HCV-Ab), serum alpha feto protein, serum insulin and measurements of insulin resistance were performed to all patients. The index of insulin resistance was calculated on the basis of fasting serum glucose and insulin according to homeostasis model assessment (HOrvtA) method; HOMAIR= fasting serum insulin (ILU/m!) X fasting serum glucose (mg/dl) / 405 (Matthews *et al.,* 1985).

Statistical analysis: Data were expressed as Mean ± SD. Differences between groups were tested' with tailed-student's test for unpaired data. For correlation analysis, Pearson's correlation coefficient was calculated. Multivariate regression analyses were performed to evaluate the association between diabetes and other parameters. A value of $P \leq 0.01$ and a value of $r \geq 0.05$ were considered significant.

3.Results

The incidence of type 2-diabetes (group I) was 76/138 (55%); most of them had HCV infection 56/76 (73.5%) and 20% had HBV infection. In contrast, most of non-diabetic patients had HBV infection 31/62(50%) and 27/62 (43.5%) had HCV infection. BMI was significantly higher in group I than group 11 (p<0.0l). Group I patients had severe liver disease (Child Pugh score C) than group 11 (p <0.00l). Serum levels of hemoglobin, platelet and albumin were significantly ower, while serum levels of bilirubin, ALT, AST, FBS, PPBS, creatinine, HbA1c, alpha feto protein and HOMA IR were significantly higher in group I (Table 1).

Upper GIT bleeding, hepatic encephalopathy, hepatorenal syndrome, SBP, HCC and death were significantly higher in group I, while no significant difference was detected in the incidence of ascites (p <0.0l) for all (Table 2).

Using multiple regression analysis the following variables were predictors of death in patients with liyer cirrhosis; high serum levels of HbA1c (OR=4.5j 95% CI=2.5-9.5, r=0.680, p <0.0l), Child-Pugh class C (OR=4.5, 95% CI=2.2-8.5, r=0.620, p <0.01) low serum levels of albumin (OR=3.13,. 95% CI=1.3-5.7, r=0.580, p <0.0l) and high serum levels of creatinine (OR=3.2, 95% CI=1.1-3.2, r=0.500, p <0.0l), (Table 3).

Table (1):Clinical demographic pictures and laboratory results of studied patients.

Groups / Data	Group I with DM (n=78)	Group 11 without DM (n=62)	*P*-value
Age (years)	45±8	44±7	0.214
Sex (M/F)	43/35	38/24	0321
BMI	32±2.1	26±1.5	<0.01
Etiology			
HBS	15/76 (20%)	31/62 (50%)	<0.01
HCV	56/76 (73.5%)	27/62 (43.5%)	<0.01
Cryptogenic	5/76 (6.5%)		0.547
Child-Pugh classification			
A	12/76 (15.5%)	35/62 (56.5%)	<0.01
B	20/76 (26.5%)	15/62 (24%)	0.325
C	44/76 (58%)	12/62 (19.5%)	<0.001
Hemoglobin (gldl)	10.2±1.1	12.2±0.5	<0.01
Platelets (103/mm3)	120±10	160±21	<0.01
WBc (103/mm3)	4.2±1.0	4.5±1.1	0.150
PT (second)	16.2±1.2	13.5±0.5	<0.01
Creatinine	2.2±0.5	1.1±0.2	<0.01
Serum albumin (gldl)	3.2±0.5	4.1±0.6	<0.01
Total bilirubin (mg/dl)	2.2±0.5	1.3±0.2	<0.01
ALT (UIL)	85±12	58±6	<0.001
AST (UIL)	82±14	52±8	<0.001
FBS (mgldl)	170±20	102±8	<0.001
PPBS (mg/dl)	230±25	110±6	<0.001
HbA1c	8.5±1.1	5.2±0.5	<0.001
Alpha feto protein	80.5±15	15.5±5	<0.001
HOMA (IR)	12.5±.8	3 .2: ±.2	<0.001

Table (2): Complications of liver cirrhosis in patients with and without diabetes.

Groups / Parameters	Group I with DM (0=76)	Group 11 without DM (0=62)	*P*-value
Upper GIT bleeding	12/76 (15.5%)	5/62 (8.5%)	<0.01
Encephalopathy	18/76 (23.5%)	8/62 (13%)	<0.01
Hepatorenal syndrome	6/76 (8%)	1/62 (1.6%)	<0.01
Ascites	10/76 (13%)	8/62 (13%)	0.875
SBP	8/76 (10.5%)	2/62 (3.2%)	<0.01
HCC	10/76 (13%)	3/62 (4.8%),	<0.01
Deaths	12/76 (15.5%)	3/62 (4.8%)	<0.01

SBP- spontaneous bacterial peritionitis, HCC=hepato cellular carcinoma

Table (3): Multiple regression analysis of predictors of death in patients with and without diabetes.

Analysis / Parameters	OR	. 95% CI	r-value	*p*-value
HbA1c	4.5	2.5-9.5	0.682	<0.01
Child-Pugh class C	4.2	2.2-8.5	0.620	<0.01
Serum albumin	3.8"	1.3-5.7	0.580	<0.01
Serum creatinine	3.2	1.1-3.2	0.500	<0.01
ALT-AST	1.2	0.8-0.1	0.125	0.140
Alpha feto protein	0.8	0.2-0.4	NS	0.110

4.Discussion

In the present study the prevalence of DM in patients with liver cirrhosis was 55%. Most of them had HCV infection (73.5%) and significantly increased complications and mortality rate. Many epidemiological studies have reported a higher prevalence of diabetes in subjects with liver cirrhosis especially those infected by HCV (Knobler *et al.,* 2001 and Zein *et al.,* 2005). More recently, Pazhanivel and Jayanthi. (2011) reported that the prevalence of diabetes in South Indians with cirrhosis was 17.7%. The prevalence of HCV infection appears to be higher amongst cirrhotic with diabetes. A long term prospective follow-up of patients with diabetes will provide ideal information on the natural history of diabetes and the link between HCV infection and diabetes mellitus.

The association between diabetes mellitus and cirrhosis has been speculated since decades. The hypotheses that have been put forward for this association are summarized as follows:

A) Diabetes could be the cause of associated liver disease because the nuclear and cytoplasmic glycogen deposit, fat deposit in the hepatocytes and perisinusoidal fibrosis seen in diabetes are also seen in liver cirrhosis. It has been proven that cirrhosis is a rare consequence of diabetes, but diabetes was implicated in the pathogenesis of cirrhosis, through lesions of non-alcoholic steatohepatitis (NASH) (Cruzelfeldt *et al.,* 1990). About 25-75% patients with NASH have diabetes and similarly 90% of NASH' patients have been found to be obese. In many diabetics progression of NASH to cirrhosis has been documented (Falchuk *et al.,* 1998). The known causes of chronic liver diseases like HCV infection may also coexist in diabetics and thus result in cirrhosis (Katamna *et al.,* 1997).

B) The other possibility is implication of chronic liver disease in the etiology of diabetes. Liver plays a pivotal role in the carbohydrate metabolism. This metabolism is deranged in terms of impaired glucose tolerance in about 70% 'of the cases suffering from liver cirrhosis while frank diabetes occurs in few (Bacon *et al.,* 2004). Hyperinsulinemia, insulin resistance and hyperglucagonemia characterize this abnormal glucose metabolism. These patients with chronic liver disease develop hyperglycemia with thera-peutic doses of steroids or interferon (Farbis *et al.,* 2005).

C) Thirdly, the association of chronic liver disease with diabetes may be due to common causes like alcohol, hemochromatosis and autoimmune conditions. Hepatitis Band C are common liver diseases and they tend to occur more in diabetics than in general population. Frequent parenteral exposures id diabetics may be the cause of this 'high association of HBV and HCV infections. Extra hepatic sites of viral replication, i.e. kidneys, pancreas, spleen etc. may also produce many comorbid conditions especially in relation to organ of extra hepatic manifestation (!pawlotsky *et al.,* 1995).

There are several studies pointing to possible link between HCV infection and Type 2-DM (Caroriia *et al.,* 1999). In one of the retrospective studies on 100 orthotoptic liver transplantations for end stage liver

disease, type 2-DM was found in 50% of the cases with HCV related liver cirrhosis vs. 9% in patients having liver disease unrelated to HCV (Allison *et al.,* 1994). In another study there was an increased incidence of HCV infection in 200 type 2-DM patients recruited from UK for a prospective study (Gray *et al.,* 1995).

Reports from Europe, Middle East and North America also show an increased prevalence of diabetes in patients having chronic liver disease ",hen compared to other 'chronic liver diseases like primary biliary cirrhosis, primary sclerosing cholangitis, and alcoholic liver disease or for that matter chronic HBV related disease (EI-Zayadi *et al.,* 1994). Mason *et al.* (1999) excluded all possible factors related to abnormal glucose handling. The prevalence of diabetes was found to be higher in HCV related chronic liver disease (21%) than in chronic HBV (12%). Moreover, prevalence of chroni HCV infection was much higher in diabetics (4.2%) than in controls (1.6%). Similar association was reported in advanced liver disease cases when transplant was not available.

In the present study, all cirrhotic liver complications including upper GIT bleeding, hepatic encephalopathy, hepatorenal syndrome, SBP, HCC, Child-Pugh class C and death were significantly higher in patients. Memon *et al.* (2011) reported that the presence of diabetes in cirrhotic patients especially with HCV infection increase the risk of ascites, encephalopathy and hepatocellular carcinoma.

Patients with cirrhosis and diabetes have a shorter life expectancy than do non-diabetic patients with cirrhosis, but they typically die of complications of liver disease, such as gastrointestinal hemorrhage, rather than from complications of diabetes such as cardiovascular diseases. This suggests that, in cirrhotic patients, the development of diabetes reflects a greater degree of liver failure (Holstein *et al.,* 2002).

In our study, high HbAlc, Child-Pugh class C, low serum levels of albumin and high serum levels' of creatinine were impendent predictors of death. In accordance with our study, Gmar *et al.* (2011) DM, cryptogenic etiology of cirrhosis, blood creatinine > 1.50mg/dl and Child-Pugh score C were significantly associated with death. A one year survival probability of 52% was observed in a previous report of 75 patients with liver cirrhosis and refractory ascites. Advanced age, liver cancer and DM but not Child Pugh score were independent predictors of mortality at admission (Moreau *et al.,* 2004).

The mechanisms by which DM worsens the clinical course of liver cirrhosis have not been clearly established. Firstly, DM accelerates liver fibrosis and inflammation giving rise to more severe liver failure. Secondly, DM may enhance bacterial infections in cirrhotic patients increased mortality (Cheruvattath **and Bdlan,** 2007).

Conclusions

The incidence of DM was significantly higher in cirrhotic patients (55%) and significantly increased their complications and mortality rate. The prevalence of HCV infection appeared to be higher in patients with diabetes. High HbAlc, Child-Pugh class C, low serum levels of albumin and high serum levels of creatinine were impendent predictors of death.

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