

Prevalence of Type 2 Diabetes Mellitus in patients with Chronic Liver Disease

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Abstract

Background and Purpose: The development of type 2 diabetes mellitus (T2DM) is caused by a combination of genetic factors and lifestyle factors like obesity, lack of physical activity and stress. T2DM can develop in chronic liver disease (CLD) though its actual mechanism is not fully understood. In case of hepatitis B virus (HBV) related CLD, HBV infection has been directly related to development of abnormal glucose metabolism by pancreatic islets cell injury. Development of Insulin resistance in case of hepatitis C virus (HCV) is the key pathogenesis of development of type 2 diabetes. We aimed to study the magnitude of the problem of T2DM among the patients with various types of CLD and to find out the association of diabetes mellitus with the demographic and clinical characteristics of the patient admitted in Medicine ward in Dhaka Medical College Hospital.

Methods: This was an observational cross sectional study of 60 patients admitted into department of Medicine, Dhaka Medical college hospital between June, 2013 to December, 2013. It included all patients ≥ 18 years of age and admitted with CLD. A diagnosis of CLD was made clinically by any 2 stigmata of liver disease and biochemical, ultrasonographic, endoscopic evidence of esophageal varices \pm liver biopsy.

Results: Of the total 60 CLD patients, 40 (66.7%) suffered from chronic HBV infection, 11 (18.3%) chronic HCV infection and alcoholic liver disease 5 (8.3%), Autoimmune 1 (1.7%), Wilson disease 1 (1.7%) and unknown cause were 2 (3.3%). Among the study subjects 21.67% had overt Diabetes Mellitus and it was found to be highest among those with chronic hepatitis C (36.4%) and those with chronic hepatitis B (20%) alcohol (20%). Type 2 DM was significantly higher among the CLD patients aged more than 50 years or more.

Conclusions: It can be concluded that the occurrence of diabetes and impaired glucose tolerance (IGT) could be a matter of great concern in CLD patients, indicating towards the need for regular monitoring of the glycemic status in these patients, which would have a definite role upon the treatment strategy.

Keywords: Type 2 diabetes mellitus, chronic liver disease, chronic hepatitis.

Introduction:

Diabetes that develops as a complication of chronic liver disease is known as “hepatogenous diabetes.”^{1,2} Patients acquiring diabetes as a result of cirrhosis of liver differ from typical type 2 diabetes mellitus patients by having a lower prevalence of family history of diabetes and a lower risk of macro and micro angiopathic complication.¹ In a point prevalence study, the prevalence of micro and peripheral macro angiopathy and coronary heart disease in cirrhosis with diabetes mellitus was comparable to that of controls, and was significantly lower than that observed in randomly

selected patients with T2DM.³ Numerous reports in the literature have indicated that impaired glucose tolerance (IGT) and diabetes mellitus (DM) frequently complicate chronic viral hepatitis and cirrhosis. In patients with cirrhosis of liver, the prevalence of IGT is estimated to be about 60-80%, and that of overt diabetes is about 7-15%.^{4,5}

More than 171 million people globally are affected by DM, and the figure is expected to rise up to 366 million by 2030.⁶ T2DM in South Asian, when comparing with European individuals, is 4- to 6-fold more prevalent.⁷ DM is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:⁸

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- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (Hb A1C) $\geq 6.5\%$.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above methods on a different day. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined Impaired fasting glucose (IFG) as fasting plasma glucose levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels between 140 and 199mg/dL (between 7.8 and 11.0mmol/L). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L).⁸

Liver is one of the vital and largest organs of the body. The clinical manifestations of liver injury are diverse- ranging from isolated and clinically silent laboratory abnormalities to dramatic and rapidly progressive liver failure. Association of diabetes mellitus with chronic liver disease has been recognized for over 2 decades and there is also evidence that diabetes have a higher association of chronic viral hepatitis B and C related cirrhosis than the normal population.⁹

Hepatitis B virus infection has been directly related to the development of glucose metabolism disorders secondary to pancreatic islets cell injury.¹⁰ A recent study from the 3rd National Health and Nutrition Examination Survey (NHANES -III) in United States reported a threefold greater risk of type 2 diabetes in HCV positive more than 40 years old subjects, compared to those who were HCV negative.¹¹

Several studies reported that HCV infection may also contribute to the development of diabetes, and higher prevalence of type 2 diabetes mellitus has been observed in the developed world (2% to 9. 4%) in patients with HCV infection than in those with other forms of chronic hepatitis.¹²⁻¹⁵ This association between HCV infection and diabetes was for the first time made by Allison et al. in 1994.¹⁶ Since then, a number of observational studies have been published.

There are several organized factors which influence the development of diabetes among HCV-infected patients like age, sex, family history of diabetes, African -American race, and HIV co- infection.^{17,18} Insulin resistance (IR) and diabetes can develop at any stage of HCV infection. Multiple mechanisms have been accounted for insulin resistance and development of diabetes in patients with chronic hepatitis C. It promotes IR mainly through interfering with insulin signaling pathway in hepatocytes, increasing inflammatory response with production of cytokines such as TNF alpha and IL-6 and increasing oxidative stress.¹⁹

Recently in a medical college in Kolkata, a cross sectional study on occurrence of type 2 diabetes mellitus among the patient with CLD,²⁰ among the study subjects, 58. 1% had IGT while 14% had overt DM. IGT and diabetes were significantly higher among that CLD patients aged 45 years or more ($p<0.05$). However, similar association was not observed with regard to sex of the patients. No association was found between the occurrence of overt diabetes with either severity as per Child Pugh score or duration of CLD. Another study was conducted in King Fahad Central Hospital, Saudi Arabia regarding prevalence and factors affecting occurrence of T2DM.²¹ Here Ashwani K, et al. concluded that patients with HCV related disease had a higher prevalence of T2DM compared to HBV related disease, their difference was not significant (26.3 vs 15. 7%; $p<0.05$). A strong association has been found between HCV and DM. Patient with chronic hepatitis C have an increased risk of insulin resistance & type 2 DM (Knobler, et al. 2000).²²

Li, et al. conducted a hospital-based case—control study to evaluate the role of T2DM in hepatocellular carcinoma (HCC) development in patients with CHB from January 2004 to December 2008.²³ The prevalence of Type 2 diabetes is higher among HCC patients without cirrhosis than among those with cirrhosis (12.1% vs. 6.7%, $p=0.003$). T2DM was associated with a significantly high risk of HCC in female patients after adjusting for age, family history of HCC, city of residence, hepatitis B e antigen and cirrhosis with an odds ratio (95% confidence interval, CI) of 1.9 (1.1—3.4). Restricted analyses among female patients without cirrhosis indicated that Type 2 diabetes was strongly associated with HCC risk with adjusted odds ratio (95% CI) of 5.6 (2.2—14.1). In conclusion, Type 2 diabetes is independently associated with the increased risk of HCC in female CHB patients. Female CHB patients with Type 2 diabetes are of a high HCC risk population and should be considered for HCC close surveillance program.²³

Caronia, et al. 1999 found that the prevalence of DM was higher in HCV-related cirrhosis (23.6%) than in HBV-related cirrhosis (9.4%; odds ratio [OR]. 2.78; 95% confidence interval [CI], 1.6-4.79; $P=0.0002$). 235 patients with biopsy confirmed chronic HBV or HCV underwent an oral glucose tolerance test. Only 1 of 70 patients with chronic viral hepatitis without cirrhosis was diabetic. However, 31 of 127 patients with HCV-related cirrhosis (24.4%) were diabetic compared with 3 of 38 patients with HBV related cirrhosis (7.9%, $p =0.048$). The major variables associated with NIDDM were cirrhosis (OR, 14.39; 95% CI, 1.91-108; $P=0.096$) and male sex (OR, 4.64; 95% CI, 1.32-16.18; $P=0.161$). Fasting insulin levels in 30 patients with HCV-

related cirrhosis and diabetes mellitus were elevated significantly, which was consistent with insulin resistance. However, acute insulin responsiveness was reduced in all patients with HCV infection and diabetes suggesting concomitant B-cell dysfunction. This study confirms an association between HCV and NIDDM.²⁴

Younossi et al. investigated the prevalence of DM among the patients of non-alcoholic steato hepatitis (NASH). They showed Of 132 patients with non-alcoholic fatty liver disease (NAFLD), 44 patients (33%) had an established diagnosis of DM. Patients with NAFLD and DM are at risk for the development of an aggressive outcome, such as cirrhosis and mortality.¹⁴

In a study at BIRDEM hospital of Dhaka, newly detected DM & IGT patient with elevated serum Alanine Transaminase (ALT) level was found in 8.33% case of HBsAg seropositivity in contrast to 4.17% case of anti-HCV seropositivity. Though 76.67% was NAFLD, this study reported that 3.33% had both NAFLD & HBsAg seropositivity.²⁵

CLD and type 2 diabetes mellitus are two chronic conditions which contribute to a significant morbidity and mortality. Literature is scarce regarding the occurrence of type 2 diabetes mellitus in CLD in Bangladesh. The involvement of liver in DM is well studied, but the prevalence of T2DM in CLD patients not known to be diabetic, has not been well studied. Hence present study was conducted in Dhaka medical college hospital with the objectives to study the magnitude of the problem of type 2 diabetes mellitus among the patients with various types of CLD, to find out the association of DM with the demographic and clinical characteristics of the patients.

Materials and Methods:

This was an observational cross sectional study of 60 patients admitted into Dhaka Medical College Hospital, Dhaka, from June 16, 2013 to December, 2013. Patients admitted with chronic liver disease in Medicine unit, Dhaka Medical College Hospital were included in this study. It included all patients ≥ 18 years of age with chronic liver disease, not known to be diabetic previously or not taking any drugs (like thiazides, steroid, interferon etc.) that may lead to the development of IGT. A diagnosis of CLD was made clinically by any 2 stigmata of liver disease and biochemical features suggestive of cirrhosis of liver and ultrasonographic evidence of coarse echo texture of liver parenchyma and/or endoscopic evidence of esophageal varices and liver biopsy. Confidentiality was assured and anonymity maintained. Data was collected by structured questionnaire from voluntarily participated individuals.

Result:

Total 60 cases of CLD were selected. The sample population included 48 (80%) male and 12 (20%) females with ages ranging from 18 to 70 years. Highest numbers of cases (24) were from 51-60 years age group. Regarding the occupational status, most were businessman (23.3%) in profession followed by 18.3% housewives (Table - I). Of the total 60 CLD patients, 40 (66.7%) suffered from chronic hepatitis B (HBV) infection followed by 11 (18.3%) chronic hepatitis C (HCV) infection (Table - II). Combinations of different clinical features were observed in patients with chronic liver disease. The most common presentations were abdominal swelling due to ascites (66.67%) and Jaundice (45.9%) (Table - III). The highest prevalence of DM and IGT among the patients with chronic liver diseases (CLD) was found in the 51-60 years age group (Table - IV). It was observed that 37.5%, 27.3%, 60%, of the patients with chronic liver disease due to chronic hepatitis B, chronic hepatitis C, alcoholic liver disease respectively had IGT. On the other hand occurrence of overt diabetes was found to be highest among those with chronic hepatitis C (36.4%) in comparison to chronic hepatitis B (20%) alcohol (20%) (Table - V). Only 20% had family history of DM whereas 80% of study subjects had no family history (Fig 1). Among the newly diagnosed cases of DM with CLD patients (n=13) family history of DM was present in 38.47% and 61.53% had no family history (Table-VI).

Table - I

Demographic characteristics of study subject (n=60)

Characteristics	Frequency of CLD	Percentage (%)
Age		
• 18-30	3	5.0%
• 31-40	10	16.7%
• 41-50	16	26.7%
• 51-60	24	40.0%
• 61-70	7	11.7%
Gender		
• Male	48	80.0%
• Female	12	20.0%
Profession		
• Businessman	14	23.3%
• Service holder	7	11.7%
• Teacher	4	6.7%
• Driver	4	6.7%
• House wife	11	18.3%
• Farmer	9	15.0%
• Others	11	18.3%

Table - II
Aetiology of chronic liver diseases (n=60)

Causes of CLD	Frequency	Percent (%)	Cumulative Percent (%)
HBV	40	66.7	66.7
HCV	11	18.3	85.0
Alcohol	5	8.3	93.3
autoimmune	1	1.7	95.0
Wilson's	1	1.7	96.7
Unknown	2	3.3	100.0
Total	60	100.0	

Table - III
Clinical presentation of chronic liver diseases.

Clinical presentation	Frequency of CLD	
	N	Percentage (%)
Vomiting of blood	17	28.33
Melaena	14	23.80
Ascites	40	66.67
Jaundice	27	45.09
Confusion	13	21.71
Asymptomatic	1	1.67

Table - IV
Glycemic status according to age group.

Age of patient	Euglycaemic		IGT		DM	
	Count	%	Count	%	Count	%
18-30	2	7.7	1	4.8	0	0
31-40	6	23.1	3	14.3	1	7.7
41-50	7	26.9	7	33.3	2	15.4
51-60	7	26.9	8	38.1	9	69.2
61-70	4	15.4	2	9.5	1	7.7

Table - V
Glycemic status of the study subjects as per etiology of chronic liver disease

Aetiology	Euglycaemic		IGT		DM	
	Count	%	Count	%	Count	%
HBV (n=40)	17	42.5%	15	37.5%	8	20.0%
HCV (n=11)	4	36.4%	3	27.3%	4	36.4%
Alcohol (n=5)	1	20.0%	3	60.0%	1	20.0%
Autoimmune (n=1)	1	100.0%	0	0.0%	0	0.0%
Wilson Disease (n=1)	1	100.0%	0	0.0%	0	0.0%
Unknown (n=2)	2	100.0%	0	0.0%	0	0.0%

Table - VI
Family history of DM among the patients of CLD with newly diagnosed DM (n=13).

Family history	Number cases of CLD with DM	Percent (%)
Present	5	38.47%
Absent	8	61.53%

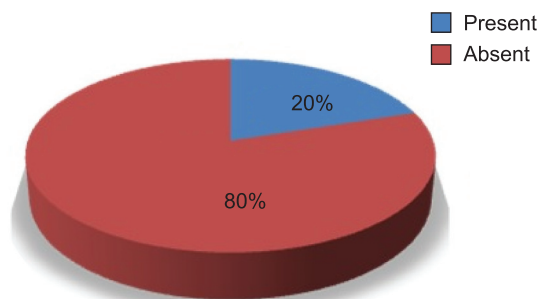


Fig 1: Family history of DM among the study subjects.

Discussion:

Association of diabetes with chronic liver diseases is not well studied in our country. But recent study reported a strong association between CLD and DM in Asian Americans, and

this association remained statistically significant after adjustment for potential confounding variables.²⁶ Their results suggested that CLD may be a potential risk factor for the development of DM among Asian Americans.

Diabetes mellitus itself may be a cause of liver disease, via non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cirrhosis and ultimately hepatocellular carcinoma.²⁷ Conversely, diabetes and IGT develop quite frequently in chronic liver disease.^{28,29} The present study was conducted to get an idea about the occurrence of DM and/or IGT among the study subjects with chronic liver diseases due to various aetiologies and not known to be diabetic.

This hospital based observational study was carried out with an aim to determine the prevalence of T2DM among the patients of CLD and also to see the association of age, sex included occupation, family history in CLD patients with DM and IGT in our country. Total 60 case of chronic liver disease were selected; among them, 40 (66.7%) suffered from chronic hepatitis B (HBV) infection, 11 (18.3%) chronic hepatitis C (HCV) infection, alcoholic liver disease 5 (8.3%), Autoimmune 1 (1.7%), Wilson disease 1 (1.7%) and unknown cause were 2 (3.3%). In a recent study Mukherjee, et al. found that 74.3% alcoholic liver diseases, 14% had chronic hepatitis B infection and 6.6% hepatitis C infection.²⁰ Compared to present study in Bangladesh alcoholic liver disease is significantly low may be due to religious bar. But due to previous sharing needle during injection and present habit of shaving and cutting hair in saloon may contribute to the very high incidence of chronic hepatitis B infection, compare to other cause of CLD. IGT was found to be quite high among the CLD patients in the present study for chronic hepatitis B 37.5%, Chronic hepatitis C 27% Alcoholic liver disease 60% it was very similar to Mukherjee et al.²⁰ Those who were glucose intolerant were, therefore, at high risk of getting frank diabetes with the passage of time.

There is a wide range in the prevalence of type 2 diabetes in CLD patients in various studies. The frequency of overt diabetes has been reported across the globe in 30-60% case.³⁰ Alavian, et al. from Iran reported that out of the total 185 enrolled CLD patients IGT was found in 11.3% and overt diabetes in 21.6%.²⁹ Another study Kobashsi et al. from Mexico reported nearly 23% prevalence of type 2 DM among the CLD patients.²⁸ The present study revealed that prevalence of type 2 diabetes mellitus was 21.67% and which is very near to above well recognized studies.

In age group 51-60 years, highest prevalence of DM (69.2%) was found in our study. Mason, et al. showed that the highest

prevalence of diabetes mellitus in 5th decade and male female ratio was almost 4:1;³¹ the findings regarding the age and sex incidence of the above study findings are consistent to current study. However, similar association is inconsistent regarding of sex of the patients according to Alavian, et al.²⁹ that found a significant association of diabetes and IGT with older age but not with sex of the CLD patients.

The etiology of liver disease is important in the incidence of type 2 diabetes; NAFLD, alcohol, HCV, hemochromatosis and autoimmune hepatitis are more frequently associated with diabetes.¹⁷ According to aetiology of CLD, prevalence of type 2 diabetes very high in HCV which was 36.4%. When we compared the prevalence of type 2 diabetes in HCV-infected population with that of HBV it was 20%, about twice. This higher rate of type 2 diabetes in HCV was consistent with Mason et al. where they reported diabetes in 21% in hepatitis C virus (HCV) infected patients as compared to 12% with hepatitis B virus infection.³¹ Qureshi et al. from Karachi, Pakistan reported an almost equal occurrence of diabetes in both HBV and HCV related liver disease.³²

White, et al. analyzed 34 eligible retrospective and prospective studies, showing a significant risk of type 2 diabetes in HCV-infected group as compared to non-HCV-infected control group.³³ On the other hand, recent data also suggest three times higher prevalence of type 2 diabetes in HCV seropositive patients.³⁴ In this way, data from the previous literature and from our study show a strong association between HCV and type 2 diabetes. Several reasons can explain the association of type 2 diabetes with HCV. One of the explanations is that the pathophysiology of HCV-associated type 2 diabetes mellitus consists of a defect in insulin secretion, increased hepatic tumor necrosis factor alpha, excessive hepatic glucose production, and insulin resistance, because the core-encoding region of HCV is sufficient to induce insulin resistance by the previously defined mechanism via either direct or indirect way.³⁵ Secondly, a major contribution of already present risk factors of diabetes such as positive family history and advancing age also plays an important role among HCV infected persons.³⁶ Advancing age (≥ 40 years) in HCV seropositive patients was significantly associated with type 2 diabetes mellitus as compared to younger age group (≥ 18 to 40 years) on both univariate and multivariate analyses. The finding also agrees with another study conducted earlier on Mexican population.³⁷

Conclusion:

There are some limitations in present study like lack of previous records of glycaemic status in few cases, small sample size, no regular follow up regarding glycaemia after

discharge. This study showed that the prevalence of DM in CLD was 21.67%. It indicates a high prevalence of DM in patients with CLD in Bangladesh. Most of the patients were in 4th to 5th decade with different occupation. Since a considerable number of diabetic patients were unaware of their problem, it is imperative that the patients should be screened for glucose intolerance periodically.

Conflict of interest: None.

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