Patients with Diabetes Mellitus are Prone to Develop Severe Hepatitis and Liver Failure due to Hepatitis Virus Infection

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Background: **Acute viral hepatitis (AVH) is usually a self-limiting illness. Diabetics are prone to develop liver diseases and liver regeneration is impaired in them. Natural course of AVH in diabetics has not been assessed and may be severe.** ***Design:*** **Observational prospective study to evaluate natural course of AVH in patients with and without diabetes mellitus. Consecutive patients with AVH were included and categorized in to those with or without diabetes. Etiology, complications, mortality and recovery parameters of AVH were identified and compared between two groups.** ***Results:*** **131 consecutive AVH between March 2007 and March 2009 were evaluated; 12 diabetics and 83 non-diabetics (n = 95) were included for analysis. Hepatitis E was the commonest cause (n = 55, 57.89%) in the whole cohort. However, Hepatitis B virus (HBV) as the etiology was significantly higher among diabetics than in non-diabetics (58.33% vs. 25.3%, P = 0.02). In contrast, hepatitis E was the etiology in 61.44% of non-diabetics. Frequency of severe hepatitis was significantly higher in diabetics than in non-diabetics (5/12; 41.67% vs. 9/83; 10.64%, P < 0.005). 5 of 14 (36%) with severe hepatitis were diabetics. Liver failure and death occurred in 2 (16%) diabetics, while none among the non-diabetics had liver failure. Multiple variable logistic regression analysis revealed that acute hepatitis B (OR 4.7 (95% CI 1.34–16.47)) and diabetes (OR 4.0 (95% CI 0.96–16.47)) were associated with severe hepatitis.** ***Conclusion:*** **Patients with diabetes are at risk to contact HBV infection and severe hepatitis. (J Clin Exp Hepatol 2013;3:275–280)**

Prevalence of diabetes mellitus worldwide is rising. It has been estimated that there would be about 366 million diabetic in the world by 2030.[1] Patients with diabetes mellitus are predisposed to develop a spectrum of liver diseases which includes fatty liver, steatohepatitis, fibrosis to cirrhosis[2,3] and hepatocellular carcinoma.[4–6] Liver regeneration capacity is impaired in animals and humans with fatty liver after partial hepatic resection.[7–9] It is therefore possible that diabetic having non-alcoholic fatty liver disease (NAFLD) may have poor regenerating capacity leading to prolonged and complicated course of acute hepatitis.[10] Analysis of database of the Department of Veterans Affairs identified diabetes as a risk factor for acute liver failure.[11]

Acute viral hepatitis (AVH) mostly has a self-limiting benign course.[12] We hypothesized that AVH would have severe and complicated course among diabetic patients. Objective, prospectively collected data on natural course of AVH among individuals with diabetes is non-existent in English literature. Therefore, the present prospective cohort study was designed to evaluate and compare natural course of AVH in patients with or without diabetes mellitus.

METHODS

Study Design

Consecutive patients with AVH attending the Gastroenterology outpatient department at the All India Institute of Medical Sciences (AIIMS), New Delhi from March 2007 to March 2009 were included. An observational design was adopted to evaluate natural course of AVH in patients with and without diabetes. Each patient included was evaluated clinically and had liver function tests (LFT), prothrombin time, complete blood count, fasting and 2-h post glucose blood sugar blood sugar levels, oral glucose tolerance test, serum lipid profile and routine grayscale real-time ultrasonography. Each patient's serum was tested for HBsAg, IgM anti-HBc, IgM anti-HAV and Anti-HCV with commercial ELISA kits (Bio-Rad, France; MBS, Italy; Xcyton, Bangalore, India respectively) using the

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Abbreviations: NAFLD: non-alcoholic fatty liver disease; AVH: acute viral hepatitis; LFT: liver function tests; ALT: alanine transaminase; HEV: hepatitis E virus; ALF: acute liver failure; BMI: body mass index; HBV: hepatitis B virus; HAV: hepatitis A virus
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manufacturer's instructions. IgM anti-HEV was performed by in-house ELISA using recombinant peptides from ORF1, ORF2 and ORF3 of the HEV genome.[13] The etiology of AVH was based on accepted conventional criteria.

All patients were followed up weekly with clinical evaluation, LFT, renal function tests and prothrombin time till they reach an end point or for 6 months duration (in case of acute hepatitis B infection).

Patients

Inclusion Criteria

All patients between 10 and 70 years, presenting with typical icteric (serum bilirubin >2 mg/dl) AVH during March 2007–March 2009, and willing to follow up weekly in the Liver clinic of AIIMS were included.

Exclusion Criteria

Patents with clinical, biochemical and/or imaging evidence of cirrhosis of liver, recent intake of hepatotoxic drugs, history of alcohol ingestion >20 g/day, suspected ischemic hepatitis, co-infection with HIV, gestational diabetes, pregnancy and hepatitis illness due to Malaria, Enteric fever, Leptospirosis and septicemia were excluded from the study. Besides, patients with associated co-morbidities which could affect survival in 6 months, such as cardiovascular disease and diabetic nephropathy, were also excluded.

Definitions and Diagnostic Criteria

Acute icteric hepatitis: was defined as acute onset jaundice with or without typical prodromal symptoms along with Alanine transaminase (ALT) levels at least > 2.5 times above the normal limit (ULN—40 IU/ml) with serum bilirubin value > 2 mg/dl.[14]

Diabetes mellitus: was diagnosed on either of following criteria (American Diabetes Association)[15]: symptoms of diabetes plus random glucose concentration ≥200 mg/dl; fasting plasma glucose ≥126 mg/dl; or a 2-h plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test.

Metabolic syndrome: was diagnosed according to Adult Treatment Panel III guidelines[16] by the presence of 3 of the following criteria: presence of fasting blood sugar >110 mg% or history of intake of antidiabetic medications; presence of hypertension with systolic blood pressure >130 mm Hg or diastolic >85 mmHg; serum triglyceride >150 mg%; serum HDL <40 mg% for men or <50 mg% for women; and a waist circumference >102 cm for men and >88 cm for women.

Definitions of Complications during Follow up

Development of ascites: was clinically suspected when there was presence of abdominal distension, shifting dullness and/or fluid thrill and was confirmed by ultrasound.

Development of spontaneous bleeding: was defined as gastrointestinal bleeding or bleeding from any other site due to coagulopathy.

Development of liver failure: Acute liver failure was defined as development of encephalopathy within 4 weeks of onset of symptoms. Subacute liver failure was defined as development of encephalopathy and/or progressive ascites between 4 and 24 weeks of onset of symptoms.[17]

Development of renal failure: was defined as the doubling of the serum creatinine to a level greater than 2.5 mg/dl in less than 2 weeks.[18]

Severe hepatitis: was defined as presence of 2 of 3 criteria: hepatic encephalopathy, serum bilirubin more than 10 mg/dl, and prothrombin time prolongation of 6 s more than control sample.[19]

Resolution of hepatitis: was defined by decline of serum bilirubin to less than 2 mg/dl with normalization of aminotransferase levels.

Primary Outcome Measure

The primary outcome measure considered were development of complications or death.

Secondary Outcome Measures

The secondary outcome measure was the duration of hepatitis, which was defined as the interval between the onset of overt icterus to resolution of acute hepatitis.

End Points

The end points of the study were either complete resolution of the acute hepatitis or development of complications or death.

Statistical Analysis

The demographic and clinical parameters were compared between patients with and without diabetes, and differences were assessed with student's "t" test, Mann–Whitney U and Chi square tests.

Severe hepatitis was considered as a dependent variable and variables like age, BMI, sex, abnormal waist–hip ratio, metabolic syndrome, diabetes, NAFLD and etiology of AVH were considered as independent variables. A univariate analysis and subsequently multiple variable logistic regression was performed. Statistical analysis was undertaken with STATA (version 9.0).

RESULTS

During The study period, 131 consecutive patients with AVH were included in the study. Seventeen of these were excluded (pregnancy = 1, systemic lupus erythematosus with lupus nephritis = 1, underlying chronic liver disease = 5, late presentation = 6, use of alcohol >20 g/*d* = 3, concomitant

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Table 1 Baseline characteristics of patients with acute viral hepatitis (n = 95).

	Variable	Non-diabetic (n = 83)	Diabetic (n = 12)	P value
1	Age (yrs)	30.36 ± 11.05	49.58 ± 13.92	<0.001
2	Male Sex: n (%)	63 (75.9)	7 (58.3)	0.196
3	Body mass index (kg/m^2)	21.87 ± 3.20	25.17 ± 2.79	0.010
4	Hypertension: no. (%)	6 (7.23)	5 (41.67)	0.004
5	Waist circumference (cm)	77.82 ± 7.92	89.17 ± 10.59	<0.001
6	Triglyceride (mg/dl) median (range)	184 (64–175)	259 (129–420)	0.186
7	HDL (mg/dl) median (range)	36 (15–49)	38 (30–59)	0.155
8	Serum bilirubin (mg/dl) median (range)	6.95 (0.4–32.6)	6.6 (2.4–9)	0.453
9	AST (U/L) median (range)	853 (24–3485)	1446 (791–3141)	0.032
10	ALT (U/L) median (range)	998.5 (26–3241)	1276 (612–2894)	0.079
11	Prothrombin time Prolongation over controls (seconds) median (range)	2 (0.4–120)	3 (0–8)	0.785

Note. Data are expressed as mean ± SD unless otherwise indicated.
All laboratory parameter values were values obtained at admission.
HDL- High density lipoprotein; AST- Aspartate transaminase; ALT- Alanine transaminase.

use of Anti-tubercular treatment = 1). Of the remaining 114, 16 were lost to follow up within 2–3 weeks of presentation and 2 had anicteric course and were excluded from final analysis. One had glucocorticoids treatment prescribed by another physician and was also excluded.

The remaining 95 patients with AVH were included in the final analysis. Of these 95, eighty-three were non-diabetic and twelve were diabetic. The demographic characteristics, liver function tests and presence of metabolic syndrome are depicted in Table 1.

Diabetic patients were significantly older (P < 0.001), had significantly higher BMI (P < 0.01) as well as waist circumference (P < 0.006) and significantly higher proportion of patients of AVH with diabetes had hypertension (P < 0.004). The mean (±SD) AST values were significantly more in diabetics, whereas the ALT values were similar in both diabetics and non-diabetics as shown in Table 1.

Hepatitis E virus (HEV) was the commonest cause of AVH in the present study. Fifty-five (58%) of the 95 patients with AVH had acute hepatitis E. HBV and HAV caused acute hepatitis in 30.5% and 12% of the patients. Two patients had dual infection due to HAV and HEV (Table 2). Despite HEV being the commonest cause in the whole cohort, frequency of acute hepatitis B was significantly higher in diabetics than in non-diabetics [7/12 (58.33%) diabetic with HBV vs. 21/83 (25.3%) non-diabetics with HBV, P = 0.02](Table 3). Even though the frequency of HEV induced acute hepatitis was more frequent in non-diabetics (61.44% in non-diabetic vs. 33.44% in diabetics), the difference was not significant.

The patients included in the present study were followed up till resolution of hepatitis. The mean duration of AVH in this cohort was 7 weeks (SD = 3 weeks). Patients with acute hepatitis B were followed for upto 6 months from the onset of symptoms. All of them cleared their infection during follow up period. Mean duration of acute icteric hepatitis was similar in diabetic and non-diabetic groups (P = 0.741; range 10 days–129 days (Table 2)).

Table 2 Etiology and outcome in patients with acute viral hepatitis (with and without diabetes mellitus).

	Non-diabetic (n = 83)	Diabetic (n = 12)	P value	Total (%) (n = 95)
Etiology				
IgM anti-HAV	11 (13.25%)	1 (8.33%)	1.0	12 (12.63)
IgM anti-HBc	21 (25.30%)	7 (58.33%)	0.02	28 (30.52)
IgM anti-HEV	51 (61.44%)	4 (33.33%)	0.12	55 (57.89)
Outcome				
Duration of complete resolution of acute hepatitis (days)	41.01 ± 22.30	41.01 ± 22.30	0.741	–
Frequency of severe hepatitis - n.(%)	9 (10.84%)	5 (41.67)	0.005	–
Frequency of Liver Failure-n.(%)	0 (0)	2 (16.67)	0.02	–

Table 3 Univariate and multivariable[a] analyses to identify factors associated with severe hepatitis.

Variables	Severe hepatitis (n = 14)	Uncomplicated hepatitis (n = 81)	P-value
Age (yrs): mean ± SD	37.57 ± 15.38	31.96 ± 12.53	0.138
BMI (kg/m^2): mean ± SD	21.82 ± 2.59	22.18 ± 3.38	0.735
Male sex: no. (%)	10 (71.43)	60 (74.07)	1.000
Abnormal waist–hip ratio: no.(%)	2 (20.00)	13 (30.23)	0.706
Metabolic syndrome: no. (%)	1 (11.11)	10 (13.70)	1.000
Diabetes: no. (%)	5 (35.71)	7 (8.64)	0.015
NAFLD: no. (%)	1 (7.14)	4 (5.0)	0.542
HBV: no. (%)	9 (64.28)	19 (23.46)	0.004
HAV: no. (%)	1 (7.14)	11 (13.58)	0.687
HEV: no. (%)	4 (28.57)	51 (62.96)	0.021

BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; HBV: hepatitis B virus; HAV: hepatitis A virus; HEV: hepatitis E virus.
[a]Multiple variable logistic regression analysis revealed presence of diabetes mellitus and acute hepatitis B infection were the only independent variable associated with severe hepatitis. Presence of diabetes mellitus had an OR of 4.022 (95% CI: 0.96–16.83), P = 0.057 and acute hepatitis B had an OR of 4.702 (CI: 1.34–16.47), P = 0.015.

Fourteen patients developed severe hepatitis. Five of these 14 (36%) patients with severe hepatitis were diabetics. Frequency of severe hepatitis was significantly higher in diabetics than in non-diabetics [5/12 (41.67%) diabetics vs. 9/83 (10.84%) non-diabetics, (P < 0.005)]. Both the patients of liver failure were female and elderly (62 and 65 years). One had hepatitis E infection while the other had acute HBV infection as the etiology. At presentation, they had serum bilirubin of 8.4 and 6.6 mg/dl, AST/ALT (U/L) values of 331/1069 and 2110/1750 and prolongation of prothrombin time by 8 and 7 s respectively. They developed encephalopathy after 45 and 10 days of onset of jaundice and died 10 and 6 days thereafter. None of the patients developed ascites or bleeding during the follow up period.

Univariate and Multiple Variable Analyses

On univariate analysis, age, sex, BMI, waist–hip ratio, metabolic syndrome, NAFLD and acute HAV infection were not significantly associated with severe hepatitis. Statistically significant association with severe hepatitis was detected with presence of diabetes (P < 0.015) and acute hepatitis B infection (P < 0.004) (Table 3).

On multiple variable logistic regression, acute hepatitis B infection had OR of 4.7 (95% CI 1.34–16.47) and diabetes had OR of 4.0 (95% CI 0.96–16.47) for association with severe hepatitis (Table 3).

DISCUSSION

AVH is usually associated with complete spontaneous clinical, biochemical and virological recovery within 4–6 weeks of onset with 1–5% of patients developing complications like acute liver failure (ALF), subacute hepatic failure or prolonged icteric course. The identified determinants of such complicated natural course include the specific viral etiology,[20] host factors such as immune competence, age of infection[21] and presence of compensated pre-existing chronic liver disease.[22–26]

In the present study, the presence of diabetes has emerged as a risk factor for complicated outcome during an episode of AVH. Two out of 12 diabetics had liver failure and death with a mortality rate of 16.67%. In contrast, none of the non-diabetics died or developed liver failure. Further, frequency of severe hepatitis was significantly higher in diabetics than in non-diabetics (P = 0.005; Table 2). Overall 36% patients with severe hepatitis were diabetic, which is markedly higher than the prevalence of diabetes in general population.[27]

In epidemic and sporadic situations, the frequency of ALF in AVH has been reported in 1–2% of the patients.[12] A frequency of more than 16% ALF among diabetics with AVH is alarming and identifies diabetes as a risk group to develop liver failure subsequent to AVH. The multivariate analysis also identified that presence of diabetes was associated with severe hepatitis. These results are also important in the context of a recent multicentre study by the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, which estimated the prevalence of diabetes in India to be 62.4 million.[28]

Previous studies have also noted that the incidence of ALF appears to be increased in patients with diabetes: 2.31 per 10,000 person-years compared with 1.44 in the background population.[11,29] It is however uncertain whether it is diabetes per se, medications for diabetes, or some unknown factor that accounts for the increased risk of ALF in diabetes mellitus.[30] However, this is the first study where severe hepatitis and liver failure in diabetics with hepatotropic viral infections have been evaluated.

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Another important observation is the more frequent occurrence of HBV associated AVH among diabetics than in non-diabetics (Table 2). About 60% cases of diabetic-AVH were due to HBV whereas about 60% of non-diabetic-AVH cases were due to HEV (Table 2). In India, 40–60% of the AVH in sporadic cases are due to HEV[31] and HBV infection accounts for about 20% of the sporadic cases.[32,33] In the present study, there were 28 patients with acute hepatitis B infection and 7 (25%) of them were diabetic. Higher proportion of diabetics (4/7 diabetics; 57%) compared to non-diabetic patients (5/21 non-diabetics; 23%) had severe hepatitis due to HBV infection and one of them died due to acute liver failure. In contrast, mortality did not occur in non-diabetics. This data would indicate that diabetics are more prone to develop acute hepatitis B virus infection and this is likely to cause severe hepatitis threatening life. It is unclear as to why frequency of acute HBV infection among diabetics would be high in an area hyperendemic for HEV. In the present study also hepatitis E was the commonest etiology of AVH in the whole cohort as well as among the non-diabetics. Frequent parenteral exposure, more often due to repeated testing and insulin therapy could be responsible for enhanced risk of HBV infection in diabetics. On multivariate analysis, diabetes had OR of 4 and acute HBV infection had OR of 4.7 for severe hepatitis. These finding would logically suggest inclusion of diabetics as routine candidates for HBV vaccination.

Insulin resistance is a key element in the pathogenesis of NAFLD and type 2 diabetes mellitus. Higher rate of severe hepatitis and ALF could be due to impaired capacity of hepatocytes to regenerate in the presence of insulin resistance as shown in patients with NAFLD undergoing partial hepatectomy[9] and experimental rat models.[34,35] However, in the present study, BMI and waist hip ratio were not associated with occurrence of severe hepatitis. These parameters were abnormal predominantly among the diabetics (Table 1) and therefore presence of diabetes as a robust predictor of development of severe hepatitis in both univariate and multivariate analysis in the present study might have masked the association of other metabolic factors with occurrence of severe hepatitis.

In conclusion, the present study has documented that patients with overt diabetes mellitus are at high risk to develop severe hepatitis as well as liver failure subsequent to AVH. Even in an area hyperendemic for hepatitis E like India, diabetics are at higher risk to contract hepatitis B virus infection. Therefore routine HBV vaccination should be recommended for diabetic patients.

CONTRIBUTIONS BY AUTHORS

KKS: Implementation, data management, analysis, draft; SKP: laboratory support; S—intellectual inputs, patient management, draft; SKA: design, concept, final write -up.

CONFLICTS OF INTEREST

All authors have none to declare.

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