Diabetes Mellitus is equally frequent in Chronic HCV and HBV Infection

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Abstract

Objective: To see the association of type 2 diabetes mellitus (Type 2 DM) in patients suffering from chronic HBV or HCV related liver disease.
Setting: Patients were selected from the gastroenterology OPD of the medical research centre, diabetic controls from private diabetes clinic and healthy controls from the blood bank of the hospital.
Methods: Patients with chronic liver disease had HBV, HCV tested using ELISA and blood sugar using a glucometer mostly as a 2 hour post prandial sample. Healthy controls had their sugar and ALT checked while donating blood and HBV, HCV were checked routinely. In diabetic controls, blood sample was taken and sera stored for HBV,HCV and ALT and later tested in batches. A random sugar of 200mg/dI was taken as diabetes. Results: Of 400 patients with chronic liver disease 302 had HCV and 98 HBV infection. Diabetes was found in 24.5% HCV and 19.4% HBV related cases (not significant). Out of 410 healthy controls 18 were HCV and 17 HBV positive. Diabetes was found in only 1 (5.6%) HCV positive control and none of the HBV positive controls. Of 196 diabetics 10 (5.1%) were HCV positive and none HBV positive. Diabetes was more frequent in patients having liver cirrhosis than in those having chronic hepatitis ($P<0.01$).
Conclusion: Diabetes is equally frequent in both HBV and HCV related disease but is significantly more in those with chronic liver disease than in controls. The pancreatic damage secondary to extrahepatic viral replication appears to be the major cause but genetic factors also need to be explored (JPMA52:280;2002).

Introduction

Association of diabetes mellitus with chronic liver disease has been recognized for over 2 decades[1] and the following hypothesis has been suggested:
As liver is involved in glucose metabolism therefore it is presumed that abnormal glucose tolerance should be seen in chronic liver disease and this was confirmed in many studies, whereas about 70% cirrhotics were found to have abnormal glucose tolerance[2-4]. Some workers think that diabetes may be the cause of coexisting liver disease because cytoplasmic glycogen deposit, fat accumulation in hepatocytes and perisinusoidal fibrosis are seen both in diabetes and cirrhosis. Recentlty diabetes has been implicated in the pathogenesis of cirrhosis through lesions of non alcoholic steatohepatitis (NASH) and progression of NASH to cirrhosis in diabetics has been reported[5,6].
There is also evidence that diabetics have a higher association of chronic Viral hepatitis C and B (HCV and HBV) related cirrhosis than the normal population; the reason being higher parenteral exposure. There is evidence that both HBV and HCV have extra hepatic sites of viral colonization resulting in extrahepatic manifestations especially of kidneys and pancreas resulting in proteinurea and diabetes[7-9].

Mason et al were the first to report the association of HCV with diabetes in a case control study[10]. They reported 21% diabetes in HCV positive vs 12% in HBV positive cirrhotics while in diabetics only 4.2% were HCV and 1.6% HBV infected. This was later confirmed by others11 and discussed in detail[12].
In Pakistan the HBV carrier and HCV exposure rates are high; being 8-10% for HBV and 4% for HC[13-16]. This study was therefore done to see the association of diabetes in patients having HBV or HCV related chronic liver disease and compare it with a diabetic cohort and healthy controls.

Patients and Methods

Chronic HBV, HCV cases

Records of patients coming for follow-up of chronic liver disease from 1996-1999 were retrieved. Patients with adequate documentation of abnormal ALT for over 6 months, positive serology of HBsAg (with or without HBeAg or FLBVDNA) and Anti HCV and blood sugar estimation were included in the study. Diabetes was confirmed if the random blood glucose level was _200 mg/dl or they were already on hypoglycaemic therapy[17]. Diagnosis of chronic liver disease was made on liver biopsy wherever available otherwise signs of decompensation like ascites, odema, endoscopic evidence of esophageal varices and laboratory evidence of low albumin and prolonged prothrombin time were taken into consideration. Risk factors for HBV and HCV infection which were recorded included IV drug abuse, blood or blood product transfusion, major surgery, haemodialysis, household contacts, sexual exposure and tattooing.
Patients with conditions predisposing to hyperglycaemia like chronic pancreatitis, carcinoma of pancreas and those on steroid therapy were excluded.

Diabetic Controls

Type 2 diabetics (Type 2 DM) attending the diabetic clinics of two diabetologists served as controls. Their blood was taken for HBsAg, anti HCV and ALT levels.

Healthy Controls

Subjects coming to blood bank for voluntary blood donation were used as healthy controls and their blood samples were checked for HBsAg, anti HCV, ALT levels and random blood sugar.

Statistical Analysis

Statistical analysis was done using chi square test.

Results

A total of 400 patients suffering from chronic liver disease fulfilled the criteria and they were finally selected for the analysis. They comprised of 263 males and 137 females with ages between 15 and 80 years (mean 42±13 years). Of the 400 cases, 302 (76%) had HCV and 98 (24%) HBV related liver disease (Table la).

Table 1a. Association of diabetes HBV, HCV in various groups.

	Chronic Liver Disease (n=400)		Blood Donors (n=410)		Type 2DM (n=196)	
	No.	%	No.	%	No.	%
HCV	302	75.5	18	4.4	10	5.1
HBV	98	24.5	17	4.1	-	-

All patients had deranged liver functions for more than 6 months for the purpose of analysis.
The risk factors for the transmission of infection were surgery in 139 cases (3 3.4%), blood transfusion in 107 (25.7%), household contact in 42 and dental treatment in 13 cases.
Seventy four (24.5%) HCV positive and 19 (19.4%) HBV positive patients were diabetic showing no significant difference in the two groups (Table ib).
A total of 410 blood donors were taken as healthy controls. Majority (96.5%) were males whose ages ranged from 18-55 years with a mean age of 27 ± 7 years. Eighteen (4.5%) donors were HCV positive and 17 (4.1%) HBV positive. None of the HBV positive donors and one (5.6%) HCV positive donor had diabetes. The association of diabetes in chronic liver disease and in controls showed a significantly high (P<0.05) occurrence of diabetes in HCV related liver disease (24.5%) than in controls (5.6%) (Table ib).

Table 1b. Association of Diabetes Mellitus in Chronic Liver Disease.

	Chronic Liver Disease (n=400)				Blood Donors (n=410)			
	HCV (n=302)		HBV (n=98)		HCV (n=18)		HBV (n=17)	
	No.	%	No.	%	No.	%	No.	%
Diabetes Mellitus	74	24.5	19	19.4	1	5.6	-	-

Of 196 Type 2DM cases; there were 83 males and 113 females with an age range of 20-82 years and a mean of 53 ± 13 years. Ten (5.1%) diabetics were HCV positive and none HBV positive. If we combine the blood donors and diabetics together and take them as controls then the association of HCV infection with diabetes mellitus is 1.8% (11 out of 606 cases). Diabetes was seen in 23 .25% patients with chronic liver disease; indicating a significantly high (P<0.001) association of diabetes in chronic HCV infection.
The association of Type 2DM to cirrhosis and chronic liver disease was also analyzed. Chronic hepatitis was present in 71 and cirrhosis in 27 HBV cases; with diabetes present in 11.3% and 40.7% cases respectively. Similarly chronic liver disease was present in 210 and cirrhosis in 108 HCV positive

cases with diabetes present in 20% and 33.3% cases respectively. A significantly high (P<0.01) association of diabetes was found in cirrhosis irrespective of the viral etiology (Table 2).

Table 2. Diabetes mellitus in Cirrhosis and Chronic liver disease.

Markers	Cirrhosis (n=135)			Chronic Liver Disease (n=265)			P-Value
	No. of Subject	Diabetes Mellitus		No. of Subject	Diabetes Mellitus		
		No.	%		No.	%	
HCV	108	36	33.3	194	38	19.6	<0.01
HBV	27	11	40.7	71	8	11.3	<0.01
Total (B and C)	135	47	34.8	265	46	17.4	<0.01

Year of diagnosis of HBV, HCV and diabetes was analyzed to see if diabetes occurred after exposure to the virus or vice versa. Of 74 diabetics who had associated HCV infection 43 (58%) had developed diabetes before the diagnosis of HCV, in 21(28%) cases the two diseases were diagnosed simultaneously and in 10 cases (13%) diabetes occurred after the diagnosis of HCV infection. Seventeen HBV cases were diabetics, of these 9 (47.3%) had developed diabetes before the onset of chronic liver disease, in 3 cases the diagnosis of the two infections was made simultaneously and in 7 (36.8%) diabetes occurred after the onset of HBV infection. These results should be interpreted with caution because year of detection does not necessarily mean year of occurrence of the disease.

Discussion

In the present study Type 2DM was present in 24.5% of HCV infected patients as compared to 19.4% with HBV infection. In the diabetic population 5% cases were HCV positive and similarly 5% controls were HCV positive.

The local data from blood banks of Karachi show a 4-6% HCV positivity rates and 4-8% HBV carrier rate These figures are confirmed in other studies too[17] showing an almost equal exposure rate to the two viruses. A 4.5% HCV positivity rate in the blood donors in this study probably reflects the 4% population exposure rates. The National Health Survey of Pakistan (NHSP) showed a 5% occurrence of diabetes mellitus in our population[18] which is further confirmed in this small study where 5% blood donors were found to be diabetic.

Mason et al reported diabetes in 21% of HCV infected patients as compared to 12% with HBV. In the diabetic cohort, 4.2% patients were HCV positive as compared to 1.6% in controls. They reported a strong association between HCV infection and diabetes. Our results are different from Mason showing an almost equal occurrence of diabetes in both HBV and HCV related liver disease. This is probably due to an almost equal exposure of hepatitis B and C virus in our community. In most of the developed countries hepatitis B has been controlled with active HBV vaccination programme therefore the occurrence of chronic HBV and its complications in these countries is very low.

In another study Type 2DM was found in 50% patients having HCV related cirrhosis compared to 9% patients with liver disease not related to HCV[19]. Similarly a higher occurrence of HCV antibodies was found in 200 Type 2DM cases recruited in UK for a prospective study[20]. A higher prevalence of

diabetes in HCV has also been reported from Europe, Middle East and North America[10,21-26]. Caronia et al[11] studied this association further and found that insulin resistance was increased and acute insulin responsiveness reduced in HCV patients indicating concomitant B cell dysfunction in these cases. This was earlier reported by other workers too[27-29]. These workers have suggested that extrahepatic site of viral replication in the pancreatic tissue is responsible for B cell damage ultimately leading to diabetes. HCV RNA has been detected in the pancreatic tissue by some workers[30]. This theory of pancreatic damage was further confirmed by Caronia et al[11] by observing more diabetes in cirrhotic population than in those having chronic liver disease. It was suggested that as cirrhosis takes a longer time to develop therefore the associated pancreatic damage also takes longer, fmally resulting in diabetes. In HBV infection the disease progression is rather fast therefore very few patients reach the level of cirrhosis and that is why diabetes is lower in this population.

In the present study diabetes was found more in cirrhotics (both HBV and HCV) than in those with chronic hepatitis confirming that a longer time is taken for damage to the pancreas resulting in more diabetes in cirrhosis than in chronic liver disease. In Pakistan HBV vaccination is still not incorporated in the EPI therefore its exposure rate still remains unchanged.

As both these viruses have extrahepatic sites of viral replication therefore both produce B cell damage finally resulting in diabetes. A longer followup on patients with HBV and HCV related cirrhosis might highlight a difference in the occurrence of these kinds of complications in two groups.

Apart from HBV vaccination which should be mandatory in all newborns in Pakistan, health education of the masses and the health care providers is also important to reduce the transmission of these two viruses. In the present study surgery and blood transfusion were the two common possible sources of the transmission of the disease (HBV, HCV) which could have been reduced by following international guidelines.

Diabetes is also a genetically transmitted disease. In Pakistan there is a trend towards intermarriages which might be playing some role in the genetic transmission of the disease. Further longitudinal studies are required to see this association.

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