ORIGINAL ARTICLE

A Study of the Association between Diabetes Mellitus and Chronic Hepatitis B Virus Infection

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ABSTRACT

Background: *Hepatitis B virus (HBV) infection and diabetes mellitus are major health problems associated with significant morbidity and mortality. The published literature suggests an association of diabetes mellitus with liver disease. However, the role of HBV infection in diabetes aetiology is still controversial. The present study was conducted to explore the veracity of this enigmatic association among Pakistani subjects.*

Methodology: *The blood samples and clinical information were collected from chronic HBV-positive patients Group 1 (n = 120), and their age and gender were matched with those of the healthy control subjects Group 2 (n = 120). Hepatitis B virus-positive patients were also subdivided into two groups; (Group 1a and Group 1b) with and without liver cirrhosis for evaluation of the prevalence of diabetes.*

Results: *The study revealed that there were statistically significant differences in the biochemical parameters in the HBV-positive and control groups. There was no correlation between diabetes and HBV with the prevalence of diabetes mellitus being similar in subjects with and without HBsAg (11.7% in the positive group and 10% in the controls). Since there were a relatively large number (32.5%) of HBV-positive patients with liver cirrhosis, a comparison of biochemical parameters was also carried out to evaluate the extent of the liver damage and its association with diabetes. During the comparison of HBV patients with and without cirrhosis for the prevalence of diabetes, no aetiologic association was found with diabetes.*

Conclusion: *Study revealed that there was no correlation between HBV infection and diabetes despite the significantly different biochemical parameters in the HBV-infected group and control subjects.*

Keywords: Cirrhosis, diabetes mellitus, hepatitis B, liver disease

Un Estudio de la Asociación entre la Diabetes Mellitus y la Infección Crónica por el Virus de la Hepatitis B

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RESUMEN

Antecedentes: *La infección por el virus de la hepatitis B (VHB) y la diabetes mellitus son problemas de salud importantes asociados con morbilidad y mortalidad significativas. La literatura*

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publicada sugiere una asociación de la diabetes mellitus con las enfermedades hepáticas. Sin embargo, el papel de la infección por VHB en la etiología de diabetes sigue siendo contro-versial. El presente estudio fue conducido con el propósito de explorar la veracidad de esta enigmática asociación entre sujetos paquistaníes.

Metodología: *Se recogieron muestras de sangre e información clínica de pacientes crónicos VHB positivos Grupo 1 (n = 120), y su edad y género fueron comparados con los de los sujetos sanos del control Grupo 2 (n = 120). Los pacientes positivos al virus de la hepatitis B también se subdividieron en dos grupos, a saber, (Grupo 1a y Grupo 1b) con y sin cirrosis hepática en relación con la prevalencia de la diabetes.*

Resultados: *El estudio reveló que hubo diferencias significativas en estos dos grupos en los parámetros bioquímicos entre el grupo de control y el grupo VHB positivo. En estos dos grupos no hubo correlación entre la diabetes y el VHB. Puesto que hubo un número relativamente grande (32.5%) de pacientes VHB positivos con cirrosis hepática, se realizó también una comparación de los parámetros bioquímicos a fin de comprender el grado del daño hepático y su asociación con la diabetes. Durante la comparación de los pacientes con VHB con y sin cirrosis en relación con la prevalencia de diabetes, no se halló asociación etiológica con la diabetes.*

Conclusión: *Este estudio reveló que no hubo correlación entre la infección por VHB y la diabetes, a pesar de los parámetros bioquímicos significativamente diferentes entre el grupo infectado por el VHB y los sujetos del control.*

Palabras clave: Cirrosis, diabetes mellitus, hepatitis B, enfermedad hepática

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INTRODUCTION

Hepatitis B virus (HBV) infection and diabetes mellitus are the major health problems throughout the globe (1). Hepatitis B virus infects the liver cells leading to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Globally, year 500 000 to 1.2 million people die every year due to complications of HBV infection. It is the 10th leading cause of death worldwide (2–4). Although HBV infection is prevalent all over the world, its prevalence is much higher and varies in the different areas of the Asia-Pacific region (3).

Diabetes is a common and complex metabolic disorder characterized by abnormally elevated blood glucose levels. It is a non-communicable chronic disease that has considerable mortality both in the developed and the developing nations (5). There were 151 million diabetics in 2000 and it is predicted that in 2025 there will be 324 million people with diabetes (6). The defect in insulin secretion or insulin action leads to diabetes. Damage to different organs especially the kidneys, the heart, the blood vessels and the eyes is the eventual outcome of chronic hyperglycaemia (7).

The liver is a vital organ of the body and plays a central role in carbohydrate, fat and protein metabolism. It is involved in glucose homoeostasis through glucose storage in the form of glycogen, the conversion of glycogen to glucose when required and the production of glucose from non-carbohydrate sources (8). Some disorders of the liver like haemochromatosis and fatty liver disease can lead to diabetes mellitus (9, 10). Glucose intolerance and diabetes mellitus are prevalent in chronic liver disease especially in liver cirrhosis (11). The decreased binding of insulin to the target tissues and insufficient insulin secretion from β-cells, are the main causes of insulin resistance, which leads to glucose intolerance in cirrhotic patients. The prevalence of impaired glucose tolerance and diabetes mellitus is 20–50% in cirrhotic patients (12). It is also reported that the risk of developing chronic liver diseases and HCC increases with diabetes mellitus (9). Therefore, diabetes and liver diseases are closely associated. However, the association of diabetes and HBV infection is controversial. In a study in United States of America (USA) among HBV-infected patients, there was no increase in the prevalence of Type 2 diabetes (13). In another study in the USA, the prevalence of diabetes was higher in persons with HBV infection than among the control group.

Hepatitis B virus infection was strongly associated with diabetes mellitus among Asian Americans but not in Pacific Islanders (14). In Pakistan, no such data have been published on the association of diabetes mellitus and HBV. Therefore, we designed this study to investigate the relationship between diabetes mellitus and chronic HBV infection studying the epidemiological and clinical aspects of these diseases in Pakistani subjects.

SUBJECTS AND METHODS

Subjects

This study was carried out with 120 chronic HBV-infected patients Group 1 (the experimental group), and 120 age and gender matched subjects Group 2 (the control group) without HBV/HCV infection. All the samples were collected from Sheikh Zayed Hospital, Lahore and Aziz Fatima Hospital, Faisalabad. The epidemiological data were obtained from the patients by interviewing them at the time of the sampling and/or from their hospital records. A detailed questionnaire was prepared for this purpose before carrying out this study. The information from the patients regarding their age, gender, marital status, weight, height, body mass index (BMI), education, occupation, monthly income, physical activity, medication, family history, disease duration and complications was obtained. All subjects gave their consent for inclusion in this study.

Study Design

The HBV-infected patients were negative for anti-HCV antibodies while the control group subjects were negative for HBsAg and anti-HCV antibodies. The individuals included in this study were above 35 years of age. The diagnosis of chronic HBV infection was based on HBsAg positivity for at least six months. The diagnosis of diabetes mellitus was based on two or more readings of random blood sugar levels of > 200 mg/dL or fasting blood sugar levels of > 126 mg/dL or use of medications for diabetes (oral hypoglycaemic agents and/or insulin). Subjects with a previous history of alcohol use, steroid therapy, interferon therapy, chronic pancreatitis and haemochromatosis were excluded from the study.

Blood Collection

From each participant 5–6 mL blood were collected in two vacutainers. The serum was separated after immediate centrifugation and stored at – 20 °C.

Serological and biochemical

The subjects' hepatitis B surface antigen (HBsAg) was confirmed by ELISA using Bioelisa HBsAg colour kit (Biokit: Barcelona Spain). Their biochemical parameters were measured using Merck kits on a semi-automated clinical chemistry analyser, Microlab 300 (Merck, Germany). Their data were statistically analysed by MS Excel (R) 2007 and GraphPad InStat (R) Ver. 3.05. The association of diabetes mellitus with HBV infection was calculated using the Chi-square test and the biochemical parameters using two-tailed *t*-test. The *p*-value less than 0.05 was taken as statistically significant.

RESULTS

Demographic findings

The demographic findings of this study showed that in Group 1 (HBV-infected patients) there were 71 (59.2%) males and 49 (40.8%) females while in Group 2 (healthy control subjects) 69 (57.5%) were males and 51 (42.5%) were females. The average age of the HBV-infected patients was 50.3 ± 8.2 (Mean ± SD) compared with the average age of the healthy subjects that was 48.9 ± 7.7 (Mean ± SD).

The Prevalence of diabetes in HBV patients: The prevalence of diabetes mellitus did not differ statistically (p = 0.8) between Group 1 (14/120 or 11.7%) and Group 2 (12/120 or 10%) as shown in Table 1. The subjects 'mean body mass index (BMI) was significantly decreased (26.5 ± 2.5 *vs* 28 ± 3.1, p = < 0.0001) in Group 1 as compared with Group 2, respectively. The mean random blood glucose level was not significantly different between Group 1 and Group 2 with (165 ± 95 *vs* 149 ± 67, p = 0.1331), respectively.

Table 1: Prevalence of diabetes in HBV-infected and control group subjects

Titles	HBV-Positive (Group 1)	Control (Group 2)	Total
Number of subjects with diabetes	14	12	26
Number of subjects without diabetes	106	108	214
Total	120	120	

p = 0.8 (Chi-square test).

Biochemical findings:

The mean total serum protein value was significantly decreased (7.2 ± 0.5 *vs* 7.7 ± 0.3, p = < 0.0001) in Group

1 than Group 2. The levels of serum albumin in Group 1 were significantly low (3.9 ± 0.8 *vs* 4.6 ± 0.3, $p = < 0.0001$) as compared with Group 2. The mean value for alkaline phosphatase (ALP) was increased significantly (291.3 ± 144 *vs* 149 ± 30, $p = < 0.0001$) in Group 1 than Group 2. A significantly higher mean value of ALT (82 ± 98 *vs* 23 ± 7, $p = < 0.0001$) and AST (78 ± 96 *vs* 22 ± 8, $p = < 0.0001$) was observed in Group 1 compared to Group 2. The levels of total bilirubin (1.7 ± 1.6 *vs* 0.4 ± 0.1, $p = < 0.0001$) and direct bilirubin (0.7 ± 0.8 *vs* 0.1 ± 0.02, $p = < 0.0001$) were also significantly higher in Group 1 compared with Group 2. The demographic, anthropometric and biochemical variables in the HBV-infected patients and the control group subjects are given in Table 2. Further sub-grouping was made among the HBV-infected patients (Group 1) into cirrhosis (n = 39, Group 1a) and non-cirrhosis (n = 81, Group 1b) groups. The analysis of these groups revealed that there were 29 (74.4%) male and 10 females (25.6%) among the cirrhosis group while in non-cirrhosis group the males and females were 42 (51.9%) and 39 (48.1%), respectively. The prevalence of diabetes mellitus was 20.5% in cirrhosis patients and 7.4% in the non-cirrhosis patients. However, there was no statistical correlation between the prevalence of diabetes mellitus and cirrhotic and non-cirrhotic subjects. Therefore, cirrhosis was not found as a cause of diabetes mellitus in this study Table 3.

Table 2: Comparison of demographic, anthropometric and biochemical variables in HBV-infected patients and control group subjects

Number		HBV Positive (Group 1) 120	Controls (Group 2) 120	*p*-value	Remarks
Gender	Male	71 (59.2%)	69 (57.5%)		
	Female	49 (40.8%)	51 (42.5%)		
Mean age (years)		50.3 ± 8.2	48.9 ± 7.7		
BMI (kg/m^2)		26.5 ± 2.5	28 ± 3.1	<0.0001	Significant
Glucose (mg/dL)		165 ± 95	149 ± 67	0.1331	Non-significant
Total Protein (g/dL)		7.2 ± 0.5	7.7 ± 0.3	<0.0001	Significant
Albumin (g/dL)		3.9 ± 0.8	4.6 ± 0.3	<0.0001	Significant
ALP (U/L)		291 ± 144	149 ± 30	<0.0001	Significant
ALT (U/L)		82 ± 98	23 ± 7	<0.0001	Significant
AST (U/L)		78 ± 96	22 ± 8	<0.0001	Significant
Total Bilirubin (mg/dL)		1.7 ± 1.6	0.4 ± 0.1	<0.0001	Significant
Direct Bilirubin (mg/dL)		0.7 ± 0.8	0.1 ± 0.02	<0.0001	Significant

Quantitative values are expressed as mean ± SD.
(Two-tailed *t*-test, *p*-value < 0.05 was considered significant)
ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase

The mean age of the cirrhotic patients and non-cirrhotic patients was 56 ± 7.2 and 47.6 ± 7.3, respectively. The mean BMI in the cirrhotic patients was 25.6 ± 2.2 as compared with the 26.9 ± 2.5 in the non-cirrhotic patients. There was a significant difference in the mean random blood glucose level of the cirrhosis and the non-cirrhosis cases (203.9 ± 122.8 *vs* 146.7 ± 71.9, $p = 0.0096$). The levels of the mean total protein level (6.6 ± 0.3 *vs* 7.5 ± 2.2, $p = < 0.0001$) and mean serum albumin level (2.9 ± 0.2 *vs* 4.4 ± 0.2, $p = < 0.0001$) were significantly higher in the cirrhotic patients than in the non-cirrhotic patients. The mean ALP level was significantly lower in the cirrhosis group than in the non-cirrhosis group (423 ± 67 *vs* 228 ± 128, $p = < 0.0001$). The mean ALT level (130 ± 29 *vs* 60 ± 111, $p = < 0.0001$) and mean AST level (123 ± 25 *vs* 56 ± 109, $p = < 0.0001$) were also significantly higher in the cirrhotic patients than

Table 3: Association of diabetes with and without liver cirrhosis in HBV-infected patients

Titles	HBV positive with cirrhosis (Group 1a)	HBV positive without cirrhosis (Group 1b)	Total
Number of subjects with diabetes	8	6	14
Number of subjects without diabetes	31	75	106
Total	39	81	120

$p = 0.0733$ (Chi-square test)

Table 4: Comparison of demographic, anthropometric and biochemical variables of HBV-infected patients with and without liver cirrhosis.

		HBV positive with cirrhosis (Group 1a)	HBV-positive without cirrhosis (Group 1b)	*p*	Remarks
Number		39	81		
Gender	Male	29 (74.36%)	42 (51.85%)		
	Female	10 (25.64%)	39 (48.15%)		
Mean age (years)		56 ± 7.2	47.6 ± 7.3		
BMI (kg/m^2)		25.6 ± 2.2	26.9 ± 2.5	0.0048	Significant
Glucose (mg/dL)		204 ± 123	147 ± 72	0.0099	Significant
Total Protein (g/dL)		6.6 ± 0.3	7.5 ± 2.2	<0.0001	Significant
Albumin (g/dL)		2.9 ± 0.2	4.4 ± 0.2	<0.0001	Significant
ALP (U/L)		423 ± 67	228 ± 128	<0.0001	Significant
ALT (U/L)		130 ± 29	60 ± 111	<0.0001	Significant
AST (U/L)		123 ± 25	56 ± 109	<0.0001	Significant
Total Bilirubin (mg/dL)		3.9 ± 0.8	0.6 ± 0.2	<0.0001	Significant
Direct Bilirubin (mg/dL)		1.7 ± 0.4	0.2 ± 0.1	<0.0001	Significant

Quantitative values are expressed as mean ± SD.

in the non-cirrhotic patients, respectively. The levels of mean total bilirubin (3.9 ± 0.8 *vs* 0.6 ± 0.2, $p = < 0.0001$) and the mean direct bilirubin (1.7 ± 0.4 *vs* 0.2 ± 0.1, $p = < 0.0001$), were significantly higher in the patients with cirrhosis than those without cirrhosis.

DISCUSSION

During this study, an association of HBV infection and diabetes mellitus was evaluated to determine whether HBV infection has any role in diabetes mellitus aetiology. Hepatitis B virus infects the liver, the primary organ involved in the glucose metabolism and its storage in the form of glycogen. Therefore, the question for this study was, "Does hepatocyte infection by HBV leads to any clinical abnormality which may lead to diabetes mellitus pathogenesis owing to the impaired utilization of blood glucose?"

An analysis of biochemical parameters including enzymes for the liver function tests (LFTs), demonstrated an elevation in ALT and AST levels in the HBV-infected patients, Giannini *et al* (8) noted that altered ALT and AST were observed in patients with viral hepatitis, ischaemic liver injury, acute alcoholic hepatitis, autoimmune hepatitis, liver cirrhosis and liver damage due to drugs or chemicals such as acetaminophen over-dose, exposure to carbon tetrachloride or lead poisoning. According to Elgouhari *et al* (1), the clinical course of the chronic HBV infection is variable, although the elevation in the serum ALT levels is the characteristic feature in most cases. Furthermore, it was reported that the ALT level might be normal in some phases of the chronic HBV infection but could be followed by inter-mittent or persistent elevation.

Moreover, the raised serum ALP level among the HBV patients in this study was also similar to finding in previous studies showing an elevation in the serum ALP in active liver disease in chronically HBV-infected patients. The elevated ALP levels in the present study could also be due to the blockage in the bile ducts (obstructive jaundice), gallstones, hepatocellular carcinoma and the cancer of other organs which had infiltrated into liver. Furthermore, elevated ALP levels could also be due to bone disorders like Paget's disease, rickets, osteomalacia, bone tumours, normal bone healing and hyperparathyroidism (15). Since, these parameters were not part of the design of this study, it is suggested that in future studies these parameters should also be incorporated to exclude these conditions as causes of abnormal LFTs in HBV infection.

The raised total and direct bilirubin levels in the present study among the HBV patients also indicated that bilirubin had a strong correlation with chronic liver infection. During this study, it was observed that the total protein and albumin levels were significantly decreased in the chronic HBV-infected subjects. Since albumin is synthesized in the liver and the infected liver due to HBV leads to impaired albumin synthesis, therefore, there was a decreased supply of albumin in the serum, which might be the reason for the reduced albumin levels in the serum of the HBV-infected patients. Moreover, albumin is also a bigger part of the total protein composition of the serum, so when it gets decreased the overall total protein content is also reduced in the HBV infection (16, 17).

After an evaluation of liver function tests in the HBV-infected and control group subjects and con-cluding that there was an abnormal function of liver due to the HBV infection, it was intriguing to know if this liver damage led to the development of diabetes mellitus. Blood sugar levels were analysed in the HBV-infected and the control group subjects and it was found that diabetes mellitus was present in 11.7% of the HBV-infected patients and in 10% of the control group subjects who were without the HBV infection. However, when this association was correlated statistically, it was found that there was no contribution of HBV in causing diabetes mellitus Table 1. This finding is in concordance with other studies' findings (18, 19) where these investigators also could not find any correlation between the HBV infection and diabetes mellitus. In two different studies, the prevalence of diabetes mellitus was 12% in the HBV-infected patients (20, 21). In another study in Jeddah, Saudi Arabia, the prevalence was 14.1% (22). These findings are quite similar to the results from the present study. However, the results of present study are contrary to some previous reports, which suggest an association between diabetes mellitus and HBV infection (14, 23). However, it is emphasized that the data from different studies might not be comparable as there may be differences in the age, presence or severity of liver damage, all of which are important risk factors associated with diabetes mellitus.

The present study did not find an association between diabetes mellitus and HBV infection. Although some investigators had reported this association (14, 23), which might be due to the influence of the extent of liver damage. Therefore, to explore the possibility of liver injury affecting the association of diabetes mellitus with HBV infection, the HBV-positive patients were subdivided into two

investigators had reported this association (14, 23), which might be due to the influence of the extent of liver damage. Therefore, to explore the possibility of liver injury affecting the association of diabetes mellitus with HBV infection, the HBV-positive patients were subdivided into two groups on the basis of their liver cirrhosis status *ie* with (39/120, 32.5%) and without (81/120, 67.5%) liver cirrhosis. In some studies, it had been reported that HBV or HCV related liver cirrhosis was the possible risk factor for the development of diabetes mellitus rather than HBV or HCV infection (9).

Since in liver cirrhosis liver damage is more pronounced, the biochemical parameters of these two groups were compared before investigating any association with diabetes mellitus. It was found that there was a significant difference in most of the biochemical parameters between the liver cirrhosis and non-cirrhosis patients; so, an association of diabetes mellitus in the HBV-infected patients with and without cirrhosis was explored statistically. However, it was found that there was no association between the cirrhotic and non-cirrhotic HBV-infected patients in the present study. Hence, from this study of the HBV-infected and healthy control group subjects, it was concluded that HBV infection and its related liver cirrhosis were not responsible for causing diabetes mellitus.

The blood glucose levels were not significantly different between the HBV positive patients and the control group subjects, while a statistically significant difference was found among the cirrhotic and non-cirrhotic group of HBV-infected patients. This implied that their glucose levels were impaired, when there was a marked liver damage. The ALT and AST levels were significantly elevated in HBV positive patients compared with the control group subjects. There was a wide difference in these parameters among cirrhotic and non-cirrhotic HBV patients. This suggested that these parameters were simple and non-invasive indices for the assessment of HBV-related liver damage. The prevalence of diabetes mellitus was not significantly different in the HBV positive patients and control individuals. There was no statistically significant correlation between diabetes mellitus and HBV related cirrhosis in this study. This showed that no significant association existed between HBV infection and diabetes mellitus. Further follow-up studies are needed in the patients with the chronic HBV infection to understand the development of diabetes mellitus over the passage of time in a large number of the patients.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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