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The Prevalence and Risk Factors of Type II Diabetes Mellitus Among Patients with Hepatitis B Virus: A Descriptive Correlational Study

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Abstract

Background: There are 350 million carriers of hepatitis B virus (HBV) around the world. HBV can be associated with type II diabetes mellitus. The aim of this study was to evaluate the prevalence and risk factors for type II diabetes mellitus among patients with HBV.
Methods: This community-based, cross sectional, descriptive, correlational study recruited participants above 13 years, who resided in Esfandiar rural area, Tabas, Iran. A blood sample was collected from each participant for serological and biochemical tests. A researcher-made questionnaire was used to collect data on the participants' demographic characteristics, HBV risk factors, and diabetes mellitus risk factors. Independent sample t test, Chi square test, and Fisher's exact test were applied in SPSS v. 22.0 at a significance level of < 0.05.
Results: This study was conducted on 1245 rural dwellers, with the mean age of 36.5 ± 18.5 years (range, 13 - 96 years). The study population consisted of 676 (54.3%) males and 569 (45.7%) females. The prevalence of type II diabetes mellitus and hepatitis B surface antigen (HBsAg) seropositivity was 7.6% (n, 95) and 12.5% (n, 156) among the participants, respectively. Moreover, the prevalence of HBsAg seropositivity among diabetic patients was insignificantly higher than nondiabetic patients (15.8% vs. 12.3%; $P = 0.32$). The prevalence of seropositivity among diabetic men was significantly higher than diabetic women ($P = 0.02$). The mean age, body mass index, systolic and diastolic blood pressure, waist circumference, and hemoglobin A1c level were significantly higher among diabetic, antigen-positive patients, compared to their nondiabetic counterparts ($P < 0.05$). However, these groups were not significantly different with respect to alanine aminotransferase and aspartate aminotransferase levels ($P > 0.05$).
Conclusions: This study suggests that HBV can be a risk factor for type II diabetes mellitus. Therefore, continuous monitoring for diabetes mellitus is essential for patients with HBV infection, particularly those above 50 years, those with a body mass index above 25 kg/m^2, and those with a positive family history of type II diabetes mellitus.

Keywords: Type II Diabetes Mellitus, Hepatitis B, Prevalence, Risk Factor

1. Background

Diabetes mellitus (DM) is one of the most serious systemic diseases around the world. The number of patients with type II DM was 177 million in 2002, which is estimated to reach 300 million by 2025 (1). The prevalence of type II DM is expected to increase by 69% and 20% in developing and developed countries by 2030, respectively; also, the number of diabetic patients will reach 24 million in Africa (2).

On the other hand, hepatitis B virus (HBV) infection is a serious and debilitating disease. Currently, there are 350 million carriers of HBV around the world (3). Each year, 877 000 people die due to the serious complications of HBV infection, including cirrhosis and hepatocellular carcinoma (4). The prevalence of HBV infection among Iranians below 22 and 28 years is less than 0.5% and 1%, respectively. Also, the prevalence of HBV infection is estimated at 1.6% in Southern Khorasan province, Iran (5), while its prevalence among adults ranges from 6.3% to 13.1% in this province (6).

Hepatitis and type II DM are interrelated in some ways. According to previous research, 60% of patients with cirrhosis suffer from impaired glucose tolerance, while 20% have type II DM. On the other hand, diabetic patients experience a wide range of liver problems from abnormal liver function to hepatomegaly, hepatic steatosis, and steatohepatitis (7). Overall, liver plays a significant role in glucose homeostasis. Therefore, liver inflammation and degeneration during hepatitis alter glucose metabolism.

Inflammatory mediators, such as tumor necrosis factor and nitric oxide, cause insulin dysfunction in the liver, as well as insulin resistance (8). Increased levels of tumor

necrosis factor suppress tyrosine phosphorylation in insulin receptors and cause insulin resistance (9). The replication of HBV in pancreatic cells also aggravates insulin dysfunction (9). On the other hand, insulin resistance, steatosis, and cytopathic effects of HBV can accelerate hepatic fibrosis (8).

The association of type II DM with hepatitis has been reported in different studies. In this regard, a study on 3377 individuals showed that the prevalence of hepatitis B surface antigen (HBsAg) seropositivity among diabetic patients was higher than the nondiabetic ones (21.3% vs. 15.53%) (2). Moreover, another study reported that the risk of HBV infection among diabetic patients was 1.5 times higher than nondiabetic individuals (9).

Nonetheless, some studies have reported an inverse relationship between HBV infection and DM. A study on 900 Chinese laborers with no history of DM revealed that 51.6% were positive for hepatitis B surface antibody (HBsAb) and 25% were HBsAg positive. The prevalence of DM among HBsAb-positive patients was lower than the HBsAg-positive ones (15.7% vs. 26.5%) (10). Given the contradictory results of previous research, the present study was conducted to evaluate the prevalence and risk factors for type II DM among patients with HBV infection.

2. Methods

This community-based, cross sectional, descriptive, correlational study was performed to evaluate the prevalence and risk factors for type II DM among patients with HBV in Esfandiar rural area, Tabas, Iran. This area was selected, as it reportedly has the highest prevalence of HBV in Iran. All dwellers in this area were recruited through census sampling.

We visited the participants at home, explained the aims of the study, invited them to the study, and asked them to refer to the infectious diseases research center of Birjand University of Medical Sciences (Birjand, Iran) for blood sampling. In the research center, a blood sample was collected from each individual for serological and biochemical tests, including triglyceride, cholesterol, hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), HBsAg, and hepatitis B core antibody (HBcAb); the necessary data were collected accordingly.

The data collection tool was a demographic and clinical questionnaire. It included items on the participants' age, gender, blood pressure, and risk factors for HBV and type II DM, including blood transfusion, positive family history of hepatitis, cupping therapy, drug abuse, and cigarette smoking. The questionnaire was completed for each participant through face-to-face interviews. Content validity of the questionnaire was confirmed by 3 faculty members from Birjand University of Medical Sciences, Birjand, Iran.

Blood samples were sent to a local laboratory, where a trained laboratory technician analyzed the samples primarily for total HBcAb and liver transaminase. The HBcAb test was performed using enzyme-linked immunosorbent assay (ELISA) kits. The remaining sera were transferred to Eppendorf tubes and stored at -30°C. After primary HBcAb testing, HBcAb-positive samples were analyzed for HBsAg and HbA1c. HBsAg-positive subjects were considered as having HBV. On the other hand, individuals with HbA1c above 6.5, oral antidiabetic medication use, or with blood sugar above 200 mg/dL were considered diabetic, based on the American diabetes association criteria for DM diagnosis (2).

The collected data were entered into SPSS v. 22.0 and analyzed using independent sample t test, Chi square test, and Fisher's exact test. Data are presented using descriptive statistics, such as percentage, frequency, mean, and standard deviation.

This study was approved by the institutional review board and ethics committee of Birjand University of Medical Sciences, Birjand, Iran (ethical approval code, IR.BUMS.REC1395.207). Each participant was personally informed about the aim of the study and was asked to provide an informed consent for participation.

3. Results

This study was conducted on 1245 rural dwellers, aged 36.5 $\pm$ 18.5 years (age range, 13 - 96 years). The study sample included 676 (54.3%) males and 569 (45.7%) females. The prevalence of type II DM, HBsAg positivity, and HBcAb positivity among the participants was 7.6% (n, 95), 12.5% (n, 156), and 36.9% (n, 460), respectively. The prevalence of HBsAg positivity among diabetic and nondiabetic participants was 15.8% (15 out of 95) and 12.3% (141 out of 1150), respectively. The difference between diabetic and nondiabetic subjects regarding HBsAg positivity was not significant (P = 0.32).

The findings revealed that HBsAg-positive and HBsAg-negative diabetic patients were not significantly different regarding age, body mass index (BMI), systolic and diastolic blood pressure, ALT, and HbA1c (P > 0.05). However, the level of AST was significantly higher in HBsAg-positive diabetic subjects, compared to their HBsAg-negative counterparts (P = 0.01; Table 1). Moreover, the prevalence of HBsAg positivity among male and nonsmoker diabetic patients was higher than female and smoker diabetic patients, respectively (P = 0.02). However, HBsAg positivity

among diabetic participants had no significant relationship with history of cupping therapy or drug abuse ($P > 0.05$; Table 2).

Statistical analysis revealed that the mean age, BMI, systolic and diastolic blood pressure, and waist circumference were significantly higher in diabetic participants, compared to their nondiabetic counterparts ($P < 0.05$; Table 3). Moreover, DM had a significant relationship with educational status, family history of HBV, cigarette smoking, history of hypertension, and noninjection drug abuse ($P < 0.05$; Table 3).

4. Discussion

This cross sectional, descriptive, analytical study was performed on 1245 individuals, who resided in Esfandiar rural areas, Tabas, Iran. The prevalence of type II DM was 7.6% in the study population (n, 95), and the prevalence of HBsAg positivity was 12.5% (n, 156). HBsAg positivity was more prevalent among diabetic patients (15.8%), compared to the nondiabetic ones (12.3%). Although this difference was statistically insignificant, it was of clinical importance. In addition, the prevalence of DM among male HBsAg-positive participants was significantly higher than their female counterparts. However, HBsAg positivity among diabetic patients had no significant relationship with history of cupping therapy or drug abuse.

Most earlier studies have reported a higher prevalence of DM among patients with hepatitis C virus (HCV) infection. In this regard, a study on patients with chronic liver disease showed that the prevalence of DM among HCVAb-positive and HBsAg-positive patients was 21% and 12%, respectively (11). Another study on 400 patients with a definite diagnosis of DM indicated that 2.5% suffered from HCV infection, while the prevalence of HCVAb positivity in the nondiabetic population was 1% (12). In 3 other studies, the prevalence of DM among patients with hepatitis was estimated at 14.3% (13), 2.2% (14), and 39% (15), respectively.

The association between DM and HCV infection may be attributed to insulin resistance, caused by the negative effects of HCV on the function of islet cells. Insulin resistance, in turn, facilitates lipolysis and causes the accumulation of free fatty acids in the liver. When the antioxidant capacity of the liver is low, increased levels of inflammatory cytokines in response to free fatty acid accumulation in the liver can impair mitochondrial function and result in tissue necrosis (16).

Despite the established association of HCV with DM, previous studies have reported contradictory results regarding the association of HBV with DM. In line with the present findings, most previous studies have reported a direct relationship between DM and HBV infection. In this regard, a study on 3377 Chinese people showed that HBsAg positivity was higher among diabetic patients, compared to the nondiabetic ones (21.3% vs. 15.53%) (2). Another study revealed that the association between HBsAg positivity and DM is more evident among Asians than Icelanders (22.5% vs. 7%) (17).

Moreover, a study on diabetic and nondiabetic individuals, who were referred to a diabetes clinic during 2005 - 2014, revealed that the prevalence of HBV among diabetic patients was significantly higher than nondiabetic patients (13.5% vs. 10%). Therefore, the risk of HBV infection in the former group was 1.5 times higher than the latter group (18). Some studies have also confirmed the higher prevalence of DM among diabetic patients. The prevalence of DM in HBsAg-positive versus HBsAg-negative individuals was 13.5% versus 12.5% in Thailand (19), 4.6% versus 4.3% in Africa (20), 5.1% versus 3.8% in Turkey (11), 20% versus 17.3% in Nigeria (21), and 3.4% versus 2.2% in China (10, 19, 20).

There are different explanations for the association between HBV infection and DM. One explanation is related to the direct effects of HBV on pancreatic lymphocytes, resulting in decreased insulin production. The second explanation is that in patients with HBV, protein X reduces the expression of insulin receptor proteins (22).

The third explanation is HBV-induced B lymphocyte autoimmunity and subsequent degeneration of insulin-producing islet cells. The fourth explanation pertains to the protective or predisposing effects of certain haplotypes of human leukocyte antigens (e.g., DR_2, DR_{51}, and DQB_6) on viral infections (7). Finally, diabetic patients experience frequent hospitalizations and blood sampling procedures and are consequently at a greater risk of HBV infection.

On the contrary, some studies have reported no difference in the prevalence of DM among HBsAg-positive and HBsAg-negative individuals; a lower prevalence of DM has been even reported among HBsAg-positive individuals. A study reported that the prevalence of DM among patients with positive HBsAg antibody was lower than those without the antibody (36.5% vs. 15.7%) (10). Also, a study on 108 diabetic and 108 nondiabetic subjects showed that DM prevalence was 3.7% in both groups (22). These contradictions may be due to differences in the study sample, laboratory techniques and kits for DM and hepatitis assessments, geographical spread and prevalence of DM and HBV, and stage or window period of hepatitis.

Our findings also showed that the major risk factors for DM among patients with HBV were positive family history of DM, low educational status, cigarette smoking, history of hypertension, and noninjection drug abuse. Moreover, the mean age, BMI, waist circumference, AST, ALT, and HbA1c among HBsAg-positive diabetic patients were higher than their nondiabetic counterparts.

Table 1. Numerical Demographic and Clinical Characteristics of HBsAg-Positive and HBsAg-Negative Diabetic Patients

Characteristics	All Diabetic Cases (N, 95)	HBsAg Test Results		
		Positive (N, 15)	Negative (N, 80)	P Value
Age, y	55.4 ± 14.4	57 ± 8.7	55.1 ± 15.2	0.65
Body mass index, kg/m^2	25.6 ± 5.6	25.8 ± 3.6	25.6 ± 5.9	0.89
Systolic blood pressure	12.6 ± 2.2	13.3 ± 2	12.5 ± 1.9	0.2
Diastolic blood pressure	8.1 ± 1	8.4 ± 0.92	8 ± 1.03	0.23
ALT	11.7 ± 5.4	13.8 ± 8	11.3 ± 4.8	0.12
AST	23.2 ± 8.2	28.4 ± 13	22.2 ± 6.8	0.01
HbA1c	7.04 ± 1	6.91 ± 0.58	7.06 ± 1.07	0.61

Table 2. Categorical Demographic and Clinical Characteristics of HBsAg-Positive and HBsAg-Negative Diabetic Patients

Characteristics	All Diabetic Cases (N, 95)	Diabetic Cases Based on HBsAg Test Results		
		Positive (N, 15)	Negative (N, 80)	P Value
Gender				P = 0.02
Male	38 (41.1)	10 (26.3)	28 (73.7)	
Female	57 (58.9)	5 (8.8)	52 (91.2)	
Cigarette smoking				P = 0.02
Yes	12 (12.6)	0 (0)	12 (100)	
No	83 (87.4)	15 (18.1)	68 (81.9)	
Cupping therapy				P = 0.08
Yes	20 (21.1)	6 (30)	14 (70)	
No	75 (78.9)	9 (12)	66 (88)	
Noninjection drug abuse				P = 0.11
Yes	24 (25.3)	1 (4.2)	23 (95.8)	
No	71 (74.7)	14 (19.7)	57 (80.3)	

Previous studies on patients with hepatitis have also shown significant differences between diabetic and nondiabetic individuals regarding the mean ALT level (18, 21), mean age, cirrhosis (23), mean BMI, AST, ALT, HbA1c, cholesterol, and triglyceride (24). Another study on patients with HBV showed that diabetic patients had a significantly higher mean age (47.4 vs. 57 years) and BMI (28.4 vs. 34.5 kg/m^2), compared to nondiabetic individuals (25).

In a study on patients with hepatitis in Italy, the hyperendemic area for liver disease, mean HbA1c, BMI, AST, and ALT were significantly higher among diabetic patients, compared to nondiabetic individuals (26). All these findings confirm that older age, greater BMI, and higher levels of liver enzymes and HbA1c can be risk factors for DM among patients with HBV. HbA1c, overweight, and obesity can also cause steatosis, liver tissue injury, and hepatic fibrosis, and thereby, accelerate hepatic disease. Steatosis can also cause insulin resistance and aggravate DM.

4.1. Conclusion

This study suggests that HBV can be a risk factor for type II DM. Therefore, continuous monitoring and regular assessment of DM are essential for patients with HBV, particularly those above 50 years, those with BMI above 25 kg/m^2, those with a positive family history of type II DM, and those with abnormally high levels of AST and ALT.

4.2. Limitations

One limitation of this study is that HBV diagnosis was established based on HBsAg seropositivity. Given the likelihood of occult HBV among the participants, further laboratory studies (e.g., polymerase chain reaction) for HBsAg-negative individuals can provide more reliable results. Moreover, this study was conducted on rural dwellers, who

Table 3. Comparison of Diabetic and Nondiabetic Participants Regarding the Risk Factors for HBV and Type II DM

Risk Factors	Diabetic Cases (N, 95)	Nondiabetic Cases (N, 1150)	P Value
HbA1c	7.04 ± 1	5.64 ± 0.42	P < 0.001
BMI	25.6 ± 5.6	21.9 ± 5.1	P < 0.001
Body mass index, kg/m²	55.4 ± 14.4	34.9 ± 18.5	P < 0.001
Systolic blood pressure	12.6 ± 2	11.3 ± 1.6	P < 0.001
Diastolic blood pressure	8.1 ± 1	7.3 ± 0.97	P < 0.001
Waist circumference	91.4 ± 13.6	78.8 ± 14.4	P < 0.001
ALT	11.7 ± 5.4	11.2 ± 16.9	P = 0.76
AST	23.2 ± 8.2	22.5 ± 17.9	P = 0.72
Gender			P = 0.25
Male	57 (60)	619 (53.8)	
Female	38 (40)	531 (46.2)	
Educational status			P < 0.001
Illiterate	29 (31.2)	131 (12.1)	
Primary	56 (60.2)	488 (44.9)	
Junior high	5 (5.4)	195 (18)	
High school	2 (2.2)	203 (18.7)	
University	1 (1.1)	69 (6.4)	
Family history of hepatitis			P < 0.001
Yes	15 (15.8)	63 (5.5)	
No	80 (84.2)	1087 (94.5)	
Cigarette smoking			P = 0.005
Yes	12 (12.6)	63 (5.5)	
No	83 (87.4)	1087 (94.5)	
Hypertension			P < 0.001
Yes	39 (41.1)	84 (7.3)	
No	56 (58.9)	1066 (92.7)	
Noninjection drug abuse			P < 0.001
Yes	24 (25.3)	89 (7.7)	
No	71 (74.7)	1061 (92.3)	

are usually more physically active, have healthier eating behaviors, and are less at risk of DM, compared with urban dwellers. Finally, factors involved in the high prevalence of HBV might have also affected DM development and prevalence. Further studies are needed to determine the contributing factors for the high prevalence of HBV in the study region and to identify HBV genotypes and human leukocyte antigen typing of HBV.

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