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ORIGINAL ARTICLE

Evaluation of Risk Factors and Seroprevalence of Hepatitis B and C in Diabetic Patients in Kutahya, Turkey

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ABSTRACT

Aim: To assess the prevalence of hepatitis B and C viruses among Turkish patients with type 1 and type 2 diabetes mellitus and to determine the risk factors affecting the prevalence in these patient groups.

Methods: This study included 630 diabetic and 314 nondiabetic patients. Serologic testing for anti-hepatitis C virus (anti-HCV) and HbsAg was done using a third-generation commercial enzyme-linked immunosorbent assay, and samples positive for anti-HCV and HbsAg were confirmed by a polymerase chain reaction assay. Diabetic patients were classified by HbsAg and anti-HCV status and were evaluated according to demographic features, diabetic characteristics and nondiabetic general risk factors, harmful habits, and aminotransferase (alanine aminotransferase and aspartate aminotransferase) levels.

Results: HbsAg and anti-HCV seropositivity rates were 5.1% and 3.2% in diabetic patients and were 3.8% and 1.3% in control group, respectively. There was no statistically significant difference between the 2 groups with respect to either marker. Shared risk factors for both hepatitis infections were increased aminotransferase levels and history of hospital admission. In addition, long duration of diabetes mellitus, poor diabetic regulation, and insulin treatment usage were found to relate to HbsAg, whereas a history of blood transfusions and surgical procedures were found to associate with anti-HCV seropositivity.

Conclusions: We determined that hepatitis B virus and hepatitis C virus infections were slightly but not significantly higher in diabetic patients compared with a normal population. If it is considered that different results might be obtained in various countries or even in various regions of same country, it may be concluded that multicenter and comprehensive studies are needed to elucidate true infection rates and to identify other risk factors affecting the prevalence of these infections.

Key Words: diabetes mellitus, hepatitis C prevalence, hepatitis B prevalence, risk factors

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term cellular damage, dysfunction, and failure of various organs, especially the eyes, the kidneys, the nerves, the heart, and the blood vessels.[1] The link between DM and liver disease was recognized over 30 years ago. Although the effect of diabetes on the liver has generally been explained by hepatosteatosis, it has been hypothesized that diabetic persons are more prone to acquiring hepatitis virus (in particular hepatitis C virus; HCV) infections, and for this reason, the necessity for diabetic patients to be investigated for hepatitis markers with transaminase levels has been reported.[2–7] Most of these studies have been focused on HCV prevalence in diabetic patients.[8–15]

We studied both hepatitis B virus (HBV) and HCV prevalence in this patient group and compared it with a nondiabetic healthy group. In addition, we evaluated various diabetic and nondiabetic risk factors for HCV and HBV infections in patients with DM.

MATERIALS AND METHODS

A total of 630 consecutive diabetic patients (403 female, 227 male; mean age, 56.89 ± 11.9 years) attending our internal medicine clinic between 2005 and 2007 were recruited for the study. The control group consisted of 314 nondiabetic persons (199 female, 105 male; mean age, 52.04 ± 10.13 years) attending our internal medicine clinic for checkups. Diabetic patients were grouped as

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TABLE 1. Epidemiological and Clinical Characteristics of Diabetic Patients

	Diabetic Population, n %	*Type 1, n %*	*Type 2, n %*
Patients	630	13 (2.1)	617 (97.9)
Age, yr	56.89 ± 11.9	29.85 ± 10.4	57.46 ± 11.27
Sex			
Male	227 (36)	3 (23.1)	224 (36.3)
Female	403 (64)	10 (76.9)	393 (63.7)
Diabetes duration, yr	8.69 ± 7.36	12.85 ± 8.9	7.87 ± 6.6
Treatment			
Oral diet	62 (9.8)		62 (10)
Oral agents	365 (57.9)		365 (59.2)
Insulin	203 (32.2)	13	190 (30.8)
Hb_{A1c}, %	8.20 ± 2.6	11.33 ± 3.5	8.14 ± 2.5
<7	235 (38.1)	2 (15.4)	237 (37.6)
≥7	382 (61.9)	11 (84.6)	393 (62.4)
Late complications			
Yes	414 (65.7)	8 (61.5)	406 (65.8)
No	216 (34.3)	5 (38.5)	211 (34.2)

those with type 1 DM and type 2 DM according to 2003 American Diabetes Association guidelines.[1]

Diabetic patients were asked to complete a questionnaire, carried out by face to face interviewing. This questionnaire included age, sex, duration of diabetes, mode of therapy, presence of late complications, history of transfusion, surgical procedure, and hospital admission. Body mass index (BMI) was calculated using the formula weight/length^2. All participants were stratified according to BMI by the criteria of the World Health Organization (<25 kg/m^2, normal; 25–30 kg/m^2, overweight; >30 kg/m^2, obese).

Epidemiologic and clinical characteristics of diabetic patients are shown in Table 1.

Serological tests for surface antigen of HBV (HbsAg) and antibody of HCV were studied by third-generation enzyme-linked immunosorbent assay (Beckman Coulter, Inc, Chaska, MN). Seropositivity of the serum samples for HbsAg and anti-HCV was confirmed for HBV DNA and HCV RNA by polymerase chain reaction. Hb_{A1c} levels were measured by latex immunoagglutination using a Hb_{A1c} DCA 2000 apparatus (Ramsey, MN). The cutoff value for Hb_{A1c} was determined to be 7%. If levels of Hb_{A1c} were more than 7%, it was accepted as poor diabetic control. In diabetic patients, alanine aminotransferase and aspartate aminotransferase levels were also determined using commercial reagents in an autoanalyzer by photometric method (Prestige 24; Tokyo Boeki, Tokyo, Japan). If the value of alanine aminotransferase and/or aspartate aminotransferase was >60 U/L, it was accepted as increased aminotransferases.

■ STATISTICAL ANALYSIS

The $\varkappa^2$ test was used to determine significant differences between categorical variables. Pearson correlation test was carried out among the diabetic population variables. The variables that were found to be significant ($P \leq 0.05$) in the Pearson correlation test were taken into logistic regression. Comparison of means in the 2 groups was performed by 2-way analysis of variance. The software package used for statistical analysis was Statistical Package for the Social Sciences for Windows (Release 11.0; SPSS, Inc, Chicago, IL).

■ RESULTS

Seropositivity for HbsAg and anti-HCV of 630 diabetic patients were found in 32 (5.1%) and 20 (3.2%) patients, respectively, whereas in the control group of 314 healthy subjects, these rates were 3.8% and 1.3%, respectively. There were no significant differences between diabetic and control groups in the seropositivity rate for either HbsAg ($P > 0.05$; odds ratio [OR], 0.74; 95% confidence interval [CI], 0.37–1.46) or anti-HCV ($P > 0.05$; OR, 0.39; 95% CI, 0.13–1.16). The evaluation of HbsAg and anti-HCV status according to demographic features of diabetic and control groups is shown in Table 2. There was no significant correlation among seropositivity of HbsAg–anti-HCV and age and sex.

When the HbsAg and the anti-HCV status according to the diabetic features of the patients were analyzed (Table 3), a significant correlation was found between the positivity of HbsAg and the duration of diabetes ($P = 0.044$), mode of therapy ($P = 0.003$), and levels of Hb_{A1c} ($P = 0.025$). However, no correlation was

TABLE 2. Hepatitis Markers According to Demographic Features of Diabetic and Control Groups

	HbsAg (+)			*Anti-HCV (+)*		
Study Groups	*Diabetic Patients, n (%)**	*Control, n (%)†*	*P*	*Diabetic Patients, n (%)**	*Control, n (%)†*	*P*
32 (5.1)	12 (3.8)	0.388	20 (3.2)	4 (1.3)	0.058	
Age, yr	59.8 ± 13.9	46.7 ± 8.03	0.027	58.4 ± 12.4	56.25 ± 14.82	0.661
ex						
Male	13/227 (5.7)	7/115 (6.1)	0.89	11/227 (4.8)	1/115 (0.9)	0.059
Female	19/403 (4.7)	5/199 (2.5)	0.194	9/403 (2.2)	3/199 (1.5)	0.55

*n = 630; †n = 314.
HCV, hepatitis C virus.

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TABLE 3. Hepatitis Markers According to Diabetic Features of Patients

		HBV Seroprevalence			*HCV Seroprevalence*		
Diabetic Characteristics	***N****	***HbsAg (+), n (%)***	***HbsAg (–), n (%)***	***P***	***Anti-HCV (+), n (%)***	***Anti-HCV (–), n (%)***	***P***
DM type							
Type 1	13	1 (7.7)	12 (91.3)	0.496	1 (7.7)	12 (91.3)	0.345
Type 2	617	31 (5)	586 (95)		19 (3.1)	598 (96.9)	
DM duration, yr							
<1 yr	124	4 (3.2)	120 (96.8)	0.044	6 (4.8)	118 (95.2)	0.334
1–10 yr	315	12 (3.8)	303 (96.2)		7 (2.2)	308 (97.8)	
>10 yr	191	16 (8.4)	175 (91.6)		7 (3.7)	184 (96.3)	
Treatment							
Oral diet	62	2 (3.2)	60 (96.8)	0.003	3 (4.8)	59 (95.2)	0.009
Oral agents	365	11 (3)	354 (97)		5 (1.4)	360 (98.6)	
Insulin	203	19 (9.4)	184 (90.6)		12 (5.9)	191 (31.3)	
Hb_{A1c}, %							
<7	236	6 (2.5)	230 (97.5)	0.025	5 (2.1)	231 (97.9)	0.242
≥7	394	26 (6.6)	368 (93.4)		15 (3.8)	379 (96.2)	
Late complications							
Yes	414	22 (5.3)	392 (94.7)	0.710	15 (3.6)	399 (96.6)	0.375
No	216	10 (4.6)	206 (95.4)		5 (2.3)	211 (97.7)	

*N indicates total numbers.
DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus.

found between anti-HCV seropositivity and diabetic factors except mode of therapy ($P = 0.009$).

In addition, HbsAg and anti-HCV status of patients were evaluated according to general risk factors (transfusion, hospital admission, and surgical procedure), health behavior (alcohol consumption, smoking), BMI (kg/m^2), and presence of hypertransaminase (Table 4). Of the general risk factors, only hospital admission was found to be associated with seropositivity of HbsAg, whereas transfusion, hospital admission, and surgical procedures were associated with anti-HCV seropositivity. Although the rate of HbsAg and anti-HCV positivity among alcohol consumers was higher than those of other groups, no correlation was found between health behavior and hepatitis B and C seropositivity. In addition, there was no correlation between BMI and these markers.

After diabetic patients were stratified according to the presence of increased aminotransferases and evaluated

TABLE 4. Hepatitis Markers According to Nondiabetic Risk Factors in Diabetic Patients

		HBV Seroprevalence			*HCV Seroprevalence*		
Risk Factors	***N****	***HbsAg (+), n (%)***	***HbsAg (–), n (%)***	***P***	***Anti-HCV (+), n (%)***	***Anti-HCV (–), n (%)***	***P***
Transfusion							
Yes	45	4 (8.9)	41 (91.1)	0.486	8 (17.8)	37 (82.2)	<0.001
No	585	28 (4.8)	557 (95.2)		12 (2.1)	573 (97.9)	
Hospital admission							
Yes	278	26 (9.4)	252 (90.6)	<0.001	18 (6.5)	260 (92.5)	<0.001
No	352	6 (1.7)	346 (98.3)		2 (0.6)	350 (99.4)	
Surgical procedure							
Yes	201	12 (6)	189 (94)	0.486	11 (5.5)	190 (94.5)	0.024
No	429	20 (4.7)	409 (95.3)		9 (2.1)	420 (97.9)	
Harmful habits							
Absent	544	26 (4.8)	518 (95.2)	0.097	16 (2.9)	528 (97.1)	0.179
Smoking	67	3 (4.5)	64 (95.5)		2 (3)	65 (97)	
Alcohol	19	3 (15.8)	16 (84.2)		2 (10.5)	17 (79.5)	
BMI							
Normal	82	5 (6.1)	77 (93.9)	0.804	2 (2.4)	80 (97.6)	0.702
Overweight	289	13 (4.5)	276 (95.5)		11 (3.8)	278 (96.2)	
Obese	259	14 (5.4)	245 (94.6)		7 (2.7)	252 (97.3)	
Transaminase level							
<60	587	21 (3.6)	566 (96.3)	<0.001	13 (2.2)	574 (97.8)	<0.001
>60	43	11 (25.6)	32 (74.4)		7 (16.3)	36 (84.7)	

*N indicates total numbers.
BMI, body mass index; HBC, hepatitis B virus; HCV, hepatitis C virus.

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with respect to these markers, the rates of seropositivity for both HbsAg and anti-HCV for the patients with increased aminotransferases were determined to be higher than for patients without increase aminotransferases, and significant correlation was found ($P < 0.001$).

The risk factors affecting the prevalence of HBV and HCV were evaluated by logistic regression analysis. The importance line for HBV was presence of increased aminotransferases, history of hospital admission, use of insulin treatment, high levels of Hb_{A1c}, and long duration of diabetes, respectively, whereas for HCV was history of blood transfusion, presence of increased aminotransferases, history of hospital admission, and a history of surgical procedures.

■ DISCUSSION

The prevalence of DM is approximately 2.0% to 9.4% worldwide, and the number of diabetic patients has gradually been increasing together with the increase of obesity and sedentary life style.[16] The hepatitis B surface antigen positivity rate worldwide varies from region to region (1–20%).[17] More than 170 million individuals throughout the world are infected with HCV. The overall prevalence of anti-HCV antibodies in the United States is 1.8% of the population.[18] In a seroepidemiological study carried out in Turkey, an average of 4% to 5% of the population was found to be HBsAg carriers.[19] The prevalence of Hepatitis B in Turkey is placed in the middle endemicity region at approximately 2% to 7%.[20] In western Turkey including Kutahya, HBsAg seropositivity is approximately 3% to 4%.[20] The prevalence of HCV infection was only 0.3% to 1.8% in a countrywide study within the normal population of Turkey.[21]

Although, the link between HCV infection and DM is yet still not understood, several investigators have stated that DM might be one of the extra hepatic manifestations of HCV infection[22] and might appear through metabolic changes because of hepatic steatosis,[22,23] direct effects on pancreatic cells,[22,24] or autoimmune processes.[25] Hepatitis C virus infection promotes insulin resistance, mainly through increased tumor necrosis factor production combined with enhancement of suppressor of cytokine.[26] The studies conducted to establish an association between DM and hepatitis virus infection have been of 2 kinds: besides investigating the prevalence of hepatitis in diabetic patients, the studies investigated the prevalence of DM in those patients with hepatitis.

Most of the studies in first category have focused on the prevalence of HCV infection, and in general, high prevalence has been found in diabetic patients compared with nondiabetic patients.[7,10,12,15,27,28] The rates of occurrence of HCV in diabetic and control groups in several of these studies are as follows: Simó et al.,[15] 11.5% versus 2.5%; Okan et al,[12] 7.5% versus 0.1%; Mason et al.,[10] 4.2% versus 1.6%; and Bahçecioğlu et al.,[28] 7% versus 1%.

However, Sotiropoulos et al.[25] reported a low prevalence (1.65%) of hepatitis infection in Greek diabetic patients versus a rate of 2% in the general Greek population. Gurbuz et al.[21] established that the prevalence of anti-HCV positivity in diabetic patients (1.8%) was similar to those of general population (0.3–1.8%) in Turkey. In our study, we found the rates of anti-HCV seropositivity in diabetic patients and control group to be 3.2% and 1.3%, respectively. However, there was no significant difference between the 2 groups ($P > 0.05$).

Hepatitis B virus infection, the prevalence of which was rarely researched in diabetic patients, was determined to be higher in the diabetic group than the control group (7.1% vs 1.6%; $P < 0.001$) in the study conducted by Sangiorgio et al.,[29] whereas Savagnone et al.[30] and Okan et al.[12] have found no significant difference between diabetic and control groups. In our study, seropositivity of HbsAg in the diabetic patients and a control group was 5.1% and 3.8%, respectively, although the difference between 2 groups was not statistically significant ($P > 0.05$).

The difference between our study and those of some others[12,15,29] is that we used a nondiabetic control group rather than blood donors as the control group. Patients whose HBsAg and/or anti-HCV serology was previously determined as "positive" are prohibited from donating blood. Thus, we suggest that the rate of seropositivity for both markers in blood available from blood centers are considerably lower than those of general population and thus do not reflect true rates.

We demonstrated that both HBV and HCV infection rates in diabetic patients were not affected by demographic features such as age, sex, and anthropometric measures such as BMI. However, the mean ages of diabetic patients with HBV infection were significantly higher than those in the control group ($P = 0.034$). This finding showed that DM, which seems in old age, may be a risk factor for acquiring HBV infection. In addition, our study showed that the rate of HCV infection in male diabetic patients was higher than those in the matched control group, but was not statistically significant ($P = 0.059$).

An effect of obesity on the prevalence of HBV and HCV infection in diabetic patients was not observed in this study or other studies.[10] Increased transaminase levels seen in diabetic patients are generally attributed to hepatosteatosis associated with obesity. But in our study, the presence of increased aminotransferases, regardless of BMI levels, was shown to be strongly related to the prevalence of HBV and HCV infection. Therefore, we suggest that increased aminotransferase levels may constitute an indication for investigation of both hepatitis markers. Several studies have shown that the prevalence of

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HBV and/or HCV increased in diabetic patients who had increased aminotransferases compared with those who did not[12,29]. Okan et al.[12] found that the percentage of patients with increased aminotransferase levels was 10.9%, and that the prevalence of HCV in patients with high levels of transaminase compared with those with normal values was 31.5% versus 4.5%, respectively, whereas the prevalence of HBV was 15.7% and 3.8%, respectively. Sangiorgio et al.[29] found that the percentage of patients with increased aminotransferase was 19.48%, and that 38.98% of there patients were anti-HCV positive. They also found that 16.9% were positive for Hepatitis B, whereas 19.3% were only positive for the B markers. In our study, the incidence of increased aminotransferases was found to be 6.8%, whereas the prevalence of HCV and HBV in those with increased aminotransferases compared with those without was determined to be 25.6% versus 3.6% ($P < 0.001$) for HCV and 16.3% versus 2.2% ($P < 0.001$) for HBV, respectively.

In our study, when DM-related risk factors for hepatitis markers were evaluated, the patients whose duration of diabetes was ≥ 10 years, whose Hb_{A1c} levels were ≥ 7%, and whose treatment regimen was with the use of insulin supplementation were found to clearly have a higher prevalence of HBV infection than the matched control groups. Use of insulin as a mode of therapy is associated with a long duration of diabetes and dysregulated blood sugar levels.[31] Because treatment with insulin is currently performed using disposable injectors or pens, increased HBV infection cannot clearly be attributed to nonsterilized injectors. However, this mode of therapy remains outside the observation of physicians because it is performed by family members or by the patients themselves. In addition, usually there is little knowledge about the hepatitis B status within the families of diabetic patients. A limitation of our study was that we could not investigate hepatitis markers among family members of the participants. Additionally, in our study, we could not establish whether this infection was acquired before or after development of diabetes. A long duration of diabetes may lead to the performance of more medical interventions and that may increase the risk of HBV infection. No relation between the prevalence of HCV infection and diabetic characteristics, except mode of therapy, was found. Insulin usage was also shown to be an important risk factor in patients with HCV infection similar to those with HBV infection. However, there are other studies showing an association of hepatitis virus infections with diabetes duration[12] or insulin treatment.[25]

In the studies that investigated the association between HCV infection and general risk factors unrelated to diabetes such as hospital admission, blood transfusion, and surgical procedures, Simó et al.[15] and Sotiropoulos et al.[25] found an association only with history of blood transfusion from among these 3 risk factors. Our study has shown that a significant association exists between HCV infection and each of these general risk factors unrelated to diabetes ($P < 0.05$). Nevertheless, we have not established this relation for HBV infection except for hospital admission. This finding indicates that more medical intervention carried out on diabetic patients may increase the risk of acquiring Hepatitis virus infection.

Although the data we obtained did not allow us to evaluate whether the abovementioned risk factors were present before development of DM, we propose that a consideration of these factors may be beneficial while evaluating the seropositivity of both hepatitis markers in diabetic patients.

■ CONCLUSIONS

In our study, HBV and HCV prevalence in diabetic patients compared with nondiabetic patients was found to be higher, but this difference was not statistically significant. Our data also showed that the infection rates of DM in each country and even each city may be variable, so further studies involving multiple centers and possibly even multiple countries are needed to elucidate true rates of HBV and HCV infection in diabetic patients and to identify other coexisting risk factors in diabetic patients with infection. In the present study, the statistically significant risk factors for HBV infection according to importance are as follows: (1) presence of increased aminotransferase, (2) history of hospital admission, (3) use of insulin treatment, (4) high levels of Hb_{A1c}, and (5) long duration of diabetes. The risk factors for HCV infection according to importance are the following: (1) history of blood transfusion, (2) presence of increased aminotransferase, (3) history of hospital admission, and (4) history of surgical procedure. On the basis of these findings, increased aminotransferase levels and hospital admission were found to be significant risk factors for both hepatitis infections in diabetic patients. In addition, these findings showed that blood transfusion was the most important risk factor for predicting HCV transmission.

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