ORIGINAL ARTICLE

Seroprevalence of Hepatitis B and C in Type 2 Diabetic Patients

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Background: Many reports in the literature suggest that chronic hepatitis C virus (HCV) infection is associated with diabetes, but the results are conflicting. The aim of our study was to investigate the seroprevalence of hepatitis B virus (HBV) and HCV infections in type 2 diabetes mellitus (DM) patients.

Methods: We collected 820 consecutive type 2 diabetic patients attending 2 of 5 outpatient endocrinology clinics in Far Eastern Memorial Hospital from March to July 2003. The control group consisted of 905 subjects who came for medical check-ups at the Family Medicine Department. We determined hepatitis B surface antigen (HBsAg) and anti-HCV in both groups, using third-generation microparticle enzyme immunoassay.

Results: No significant difference was found between type 2 DM patients and the control group for seropositivity of HBsAg (13.5% versus 12.4%; odds ratio [OR] = 1.09; 95% confidence interval [CI]: 0.77–1.55; $p = 0.441$), but anti-HCV seropositivity was detected in 6.8% of patients and 2.6% of the control subjects (OR = 2.87; 95% CI: 1.51–5.46; $p < 0.001$). In anti-HCV-positive DM patients, abnormal alanine aminotransferase was observed in 61.8%, compared with only 34.2% of anti-HCV-negative DM patients ($p < 0.001$). We did not observe any difference in risk factors for HCV infection between anti-HCV-positive and -negative DM patients.

Conclusion: The rate of seropositive anti-HCV is 2.8 times higher in type 2 DM patients than non-diabetic control subjects. [*J Chin Med Assoc* 2006;69(4):146–152]

Key Words: cross-sectional studies, diabetes mellitus, hepatitis, prevalence, Taiwan

Introduction

The liver is the primary site of hormone and glucose metabolism, and the intercommunication between liver and diabetes has long been recognized. The majority of patients with cirrhosis have glucose intolerance (60%) or overt diabetes mellitus (DM, 20%).[1] Additionally, diabetic patients have abnormal liver function tests,[2] hepatomegaly,[3] hepatic steatosis,[4] and steatohepatitis.[5] In 1994, Allison et al[6] reported that, among 34 hepatitis C virus (HCV)-related cirrhotic patients awaiting liver transplantation, 17 (50%) had diabetes mellitus, as opposed to only 9% of other cirrhotic patients unrelated with no HCV. During the same year, Özyilkan et al[7] noted an increased prevalence of HCV antibodies in patients with DM, especially in type 2 DM patients. Several subsequent studies also reported a link between DM and chronic HCV infection in both clinical[8–21] and community[22,23] settings. Previous studies indicated that chronic hepatitis C induced insulin resistance,[24,25] which may contribute to the fibrotic progression and subsequent development of type 2 DM.

In southern Taiwan, 2 studies have analyzed the relationship of HCV infection and type 2 DM. Wang et al[22] reported that HCV infection was moderately

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associated with type 2 diabetes in A-lein Township, Kaohsiung County, but such correlation was not found in Yuan-chang Township, Yuin-lin County.[26] Some previous studies also demonstrated a negative linkage between these 2 disorders.[27–29] To our best knowledge, there has been no prevalence study of chronic hepatitis B or C in type 2 DM patients in northern Taiwan. The objectives of this study were to estimate the seroprevalence rates of hepatitis B and C in type 2 DM patients visiting our endocrinology clinics, and to explore the risk factors for hepatitis in patients with type 2 DM.

Methods

We recruited all type 2 DM patients who consecutively attended 2 of 5 outpatient endocrinology clinics at Far Eastern Memorial Hospital (FEMH) during the period March 1, 2003, to July 31, 2003. After the aim of the study was explained to the patients, those who gave informed consent were asked to fill out a data sheet on demographics, diabetic data, and the potential risk factors for hepatitis. Body weight and height were measured and used to calculate body mass index (BMI). We also measured concentrations of alanine aminotransferase (ALT), fasting plasma glucose (FPG) (Hitachi 747 Autonomic Analyzer, Nakawork, Tokyo, Japan), and glycosylated hemoglobin (HbA_{1c}) (Primus CLC 385, Kansas, MO, USA). Serologic testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (anti-HCV) were performed using a third-generation microparticle enzyme immunoassay (Abbott Labs, Chicago, IL, USA). A total of 1,108 diabetic patients were contacted, and 820 agreed to participate in the study.

To compare the seroprevalence rates of hepatitis B and C between type 2 DM patients and patients without DM, we selected a reference group comprised of 905 subjects who came for medical check-ups at the Department of Family Medicine, FEMH, between January 2002 and September 2003. We excluded those individuals with FPG levels greater than 126 mg/dL. The information of the control group was retrieved from the medical check-up records at the Family Medicine Department. There were no major systemic diseases in the control group except for 15% and 4.2% who reported past histories of hypertension and hyperlipidemia, respectively. According to the records from medical check-ups, none had the combination of hypertension, dyslipidemia, and obesity.

Data were descriptively expressed as mean ± SD or number and percent. Comparisons between groups were made using Student's *t* test for continuous variables and Chi-square test for categorical data. A multivariate logistic regression model was used to determine the independent effect of various factors that were potentially associated with the risk of hepatitis. These factors included sociodemographic variables (age, sex, educational status, active smoking, and alcohol consumption), clinico-laboratory measurements (BMI, HbA_{1c}, and ALT), and clinical characteristics (duration of diabetes, treatment regimens, previous experiences of jaundice, hospital admission, surgical operation, blood transfusions, intravenous drug abuse, tattooing, hemodialysis, and abortion [for females only]). All tests were two-sided with an α-level of 0.05. Data were analyzed using the statistical software SPSS version 10.0 (Chicago, IL, USA).

Results

Comparisons between the diabetic patient group and the control group are shown in Table 1. Mean age, BMI, ALT, and FPG were significantly higher in the diabetic patients. Alcohol consumption was comparable between these 2 groups. There was no significant difference in HBsAg seropositivity in the diabetic patients (13.5%) and the control subjects (12.4%) ($p = 0.441$). On the other hand, anti-HCV seropositivity was detected in 56 (6.8%) diabetic patients and in 23 (2.6%) control subjects ($p < 0.001$). After adjustment for age, sex, BMI, and ALT, the odds ratios (OR) of seropositivity on HBsAg and anti-HCV in relation to type 2 DM were 1.09 (95% confidence interval [CI]: 0.77–1.55) and 2.87 (95% CI: 1.51–5.46), respectively. As the prevalence rate increased only for anti-HCV seropositivity, we limited the analysis to searching for correlates of anti-HCV seropositivity in the diabetic patients.

Table 2 presents sociodemographic variables, clinico-laboratory measurements, and clinical characteristics in relation to the risk of anti-HCV in type 2 DM patients. The distributions of all sociodemographic variables and clinical characteristics were similar between anti-HCV positive and anti-HCV negative diabetic patients. Diabetic patients, with or without anti-HCV seropositivity, were also similar in most clinico-laboratory measurements except ALT levels. Abnormal ALT (≥ 24 IU/L) was observed in 61.8% of the anti-HCV-positive diabetic patients compared to only 34.2% in anti-HCV-negative diabetic patients. Compared to anti-HCV-negative diabetic

Table 1. Comparisons between diabetic patients and control subjects

	Diabetic patients*		Control subjects*		$p^{\dagger}$
Age (yr)*	56.95 ± 11.33		53.65 ± 15.28		< 0.001
BMI*	26.08 ± 4.20		24.40 ± 3.85		< 0.001
FPG (mg/dL)*	155.29 ± 56.53		92.58 ± 12.85		< 0.001
ALT (IU/L)*	26.68 ± 26.85		22.89 ± 20.72		0.001
Sex (*n*)					
Male	428	52.21%	503	55.69%	0.159
Female	392	47.79%	402	44.31%	
HBsAg (*n*)					
Negative	709	86.46%	791	87.61%	0.441
Positive	111	13.54%	112	12.39%	
Anti-HCV (*n*)					
Negative	764	93.17%	877	97.44%	< 0.001
Positive	56	6.83%	23	2.56%	
Alcohol consumption‡ (*n*)					
No	592	73.91%	666	76.10%	0.317
Yes	208	26.11%	210	23.90%	
Total	820	100.0	905	100.0	

**Means ± SD; †estimated from Student's t test or Chi-square test; ‡inconsistencies between total number of patients and patients summed were because of missing information; ALT = alanine aminotransferase; BMI = body mass index; FPG = fasting plasma glucose; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.*

patients, anti-HCV-positive diabetic patients had significantly higher odds of having an ALT level of 24–40 (age-sex-BMI adjusted OR = 2.93, 95% CI: 1.53–5.58) or greater than 40 (age-sex-BMI adjusted OR = 3.39, 95% CI: 1.69–6.79).

Discussion

In this study, the seropositive prevalence rates of HBsAg and anti-HCV in type 2 DM patients were estimated to be 13.54% and 6.83%, respectively. In comparison, individuals in the DM group showed a 2.8 times higher rate of anti-HCV seropositivity. On the other hand, there was no significant difference in the prevalence rate of HBsAg seropositivity between type 2 diabetic patients and the reference sample.

Many previous studies, conducted in various nations, including Turkey,[7,19] the United Kingdom,[10] Spain,[11] the United States,[13] Italy,[17] and Korea,[18] also reported a higher prevalence rate of hepatitis C in diabetic patients. Interpretations of the findings from these studies, however, should be made with caution — various control groups were used in these studies, and the increased prevalence rate noted in certain studies could merely be an artifact of control selection. For example, some of the above-mentioned studies[11,17,19] selected blood donors as a control group for which the prevalence rate of hepatitis C is normally much lower.[30] Mason et al[13] collected the control group from those patients who were referred for radionuclide thyroid scans from the same clinic. The prevalence rate of antibodies to hepatitis C in thyroid illness patients is likely to be different from that of the general population.[31] In our study, the control group comprised people who came for a medical check-up in the same hospital. Type 2 DM patients in our hospital had increased risk of exposure to hepatitis C when compared with control subjects, but the seroprevalence rate of anti-HCV in our patients was still lower than in other high-risk groups noted in previous studies.[32–37]

One may argue that the reason why diabetic patients have a higher chance of exposure to hepatitis C is because of self-monitoring of blood glucose, insulin injection, and frequent hospitalization. If needle exposure increases the prevalence of HCV infection, it might also increase the prevalence of HBV infection. In our study, the prevalence rate of hepatitis B was similar to that of the control group.

Table 2. Sociodemographic variables, clinico-laboratory measurements, and clinical characteristics related to the risk of anti-HCV in type 2 DM patients

	Anti-HCV (–) *n* (%)	Anti-HCV (+) *n* (%)	Adjusted OR (95% CI)*	*P*
Sociodemographic variables				
Age (yr)				
< 40	39 (5.1)	3 (5.4)	1.0	
40–65	555 (72.6)	36 (64.3)	0.84 (0.25–2.86)	0.785
> 65	170 (22.3)	17 (30.4)	1.30 (0.36–4.66)	0.687
Sex				
Male	399 (52.2)	29 (51.8)	1.0	
Female	365 (47.8)	27 (48.2)	1.02 (0.59–1.75)	0.949
Educational status				
Primary school or lower	406 (55.8)	37 (69.8)	1.0	
Middle school or higher	322 (44.2)	16 (30.2)	0.54 (0.27–1.06)	0.141
Active smoking				
No	510 (67.8)	35 (62.5)	1.0	
Yes	242 (32.2)	21 (37.5)	1.26 (0.72–2.22)	0.460
Alcohol consumption				
No	553 (74.2)	38 (69.1)	1.0	
Yes	192 (25.8)	17 (30.9)	1.29 (0.71–2.34)	0.427
Clinico-laboratory measurements				
BMI				
< 25	318 (43.1)	27 (50.0)	1.0	
25–30	319 (43.2)	22 (40.7)	0.81 (0.45–1.46)	0.485
> 30	101 (13.7)	5 (9.3)	0.58 (0.22–1.55)	0.281
HbA_{1c} (%)				
< 7	248 (32.9)	19 (35.2)	1.0	
7–8	216 (28.6)	15 (27.8)	0.91 (0.45–1.83)	0.784
> 8	290 (38.5)	20 (37)	0.90 (0.47–1.73)	0.752
ALT (IU/L)				
< 24	498 (65.8)	21 (38.2)	1.0	
24–40	154 (20.3)	19 (34.5)	2.93 (1.53–5.58)	< 0.001
> 40	105 (13.9)	15 (27.3)	3.39 (1.69–6.79)	< 0.001
Clinical characteristics				
Duration of diabetes				
< 1 year	32 (4.5)	5 (9.1)	1.0	
> 1 year	686 (95.5)	50 (90.9)	0.37 (0.14–1.03)	0.058
Treatment regimen				
Diet control with/without OHA	594 (78.6)	41 (73.2)	1.0	
Insulin therapy with/ without OHA	192 (25.8)	17 (30.9)	1.39 (0.74–2.58)	0.305

**Separate multivariate logistic regression models with adjustment for age, sex, and BMI were used to estimate OR for individual potential risk factors; ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; HCV = hepatitis C virus; OHA = oral hypoglycemic agents; OR = odds ratio; NA = not available.*

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Table 2. Sociodemographic variables, clinico-laboratory measurements, and clinical characteristics related to the risk of anti-HCV in type 2 DM patients

	Anti-HCV (–) *n* (%)	Anti-HCV (+) *n* (%)	Adjusted OR (95% CI)*	*P*
History of jaundice				
No	733 (97.6)	54 (96.4)	1.0	
Yes	18 (2.4)	2 (3.6)	1.36 (0.30–6.12)	0.685
History of hospital admission				
No	200 (26.5)	15 (26.8)	1.0	
Yes	554 (73.5)	41 (73.2)	0.96 (0.50–1.81)	0.887
History of surgical operation				
No	328 (43.5)	21 (37.5)	1.0	
Yes	426 (56.5)	35 (62.5)	1.31 (0.73–2.34)	0.359
History of blood transfusion				
No	640 (85.0)	44 (78.6)	1.0	
Yes	113 (15.0)	12 (21.4)	1.53 (0.78–3.00)	0.218
History of intravenous drug abuse				
No	753 (100.0)	55 (100.0)	NA	
Yes	0 (0.0)	0 (0.0)		
History of tattooing				
No	658 (87.3)	46 (82.1)	1.0	
Yes	96 (12.7)	10 (17.9)	1.69 (0.77–3.69)	0.189
History of hemodialysis				
No	752 (99.9)	55 (98.2)	1.0	
Yes	1 (0.1)	1 (1.8)	13.67 (0.84–221.45)	0.134
History of abortion (females only)				
No	185 (52.4)	15 (53.6)	1.0	
Yes	168 (47.6)	13 (46.4)	0.92 (0.41–2.08)	0.845
Total	764 (100.0)	56 (100.0)		

**Separate multivariate logistic regression models with adjustment for age, sex, and BMI were used to estimate OR for individual potential risk factors; ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; HCV = hepatitis C virus; OHA = oral hypoglycemic agents; OR = odds ratio; NA = not available.*

Initially, it was thought that diabetes might be one extrahepatic manifestation of hepatitis C.[38] Indeed, a recent study reported that the virus itself, or the host inflammatory response to HCV infection, contributed to the development of insulin resistance and subsequent long-term risk of type 2 DM.[24] Other animal studies also indicated that the insulin resistance in HCV core gene transgenic mice was chiefly due to hepatic insulin resistance, induced by an elevated intrahepatic tumor necrosis factor-α through suppressing tyrosine phosphorylation of insulin receptor substrate-1.[25] Hepatic steatosis in chronic hepatitis C contributed to a morphologic expression of a cytopathic effect of HCV,[39] and it also influenced liver fibrosis progression[40,41] and ensuing worsening of insulin resistance.

Our study observed that type 2 DM patients with a high ALT level had increased seroprevalence of HCV. However, 34–75% of type 2 DM patients are associated with nonalcoholic steatohepatitis (NASH),[42] which is characterized by elevated ALT levels, so the relationship between HCV infection and high liver function tests should be made with caution. Because 34.2% of our anti-HCV-negative DM subjects also had abnormal ALT levels, we suggest that NASH may have contributed to those abnormal liver function tests.

Limitations of our study include the following factors. First, we used only microparticle enzyme immunoassay tests to determine the presence of HCV infection without supplemental recombinant immunoblot assay or HCV RNA test, which might have resulted in false-positive HCV results. However, previous studies suggested a high positive predictive value for the enzyme immunoassay test when used alone in the liver clinic population.[43,44] Second, we did not perform liver biopsies in all of our HCV-infected diabetic patients, so we do not know the exact pathologic grade and staging of chronic hepatitis C. The possible inaccurate ascertainment of HCV infection might entail a certain degree of misclassification of disease and, subsequently, introduce information bias into the study results. Such misclassification is, however, likely to be non-differential, which would normally bias the study results toward the null.[45]

The cross-sectional design of our study precluded drawing an etiopathologically causal inference between type 2 DM and the risks of HCV. A prospective cohort study is required to ascertain the chronologic sequence of acquiring HCV infection and the development of type 2 DM. Despite that, as type 2 DM is associated with a 2.8 times increased rate of hepatitis C, we have to keep in mind the possibility of HCV infection for our type 2 DM patients.

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