

Association between Different Hepatitis C Virus Genotypes Infection and Type-2 Diabetes Mellitus: A Descriptive-Analytical Study from the Northwest of Iran

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection and type 2 Diabetes Mellitus (T2DM) are among the severe threats to health care systems worldwide. Here, we investigated the association of HCV genotypes and cirrhosis with T2DM among HCV-positive patients. **Methods:** This descriptive-analytical study was performed from Jan 2017 to Jan 2018 at Sina Clinical-Educational infectious diseases ward, the reference center of infectious diseases in northwest Iran. All serology HCV-positive patients attending this center were included in the study. Forty-eight patients were included, 19 of which had a positive history of diabetes. Blood samples from patients were used for complete blood count, liver function tests, fasting blood sugar, HbA1C, HCV antibodies, and HCV genotype. Then the characteristics among patients with and without T2DM were compared. A *P*-value of less than 0.05 was considered statistically significant. **Results:** No significant difference in demographic variables were observed between patients with and without T2DM. Of 48 patients with HCV infection, 29 patients (39.58%) had T2DM. The hepatitis C infection duration among diabetic and non-diabetic patients was 9.03 ± 0.76 years and 8.53 ± 1.01 years, respectively ($P = 0.04$). Of 8 patients with cirrhosis, six patients (75%) had diabetes. The relative risk for diabetic patients with HCV infection to develop cirrhosis was 4.57 (95% CI [1.02-20.36], $P = 0.04$). The most prevalent genotype was HCV type 1 among both diabetic and non-diabetic groups. No significant association was observed in logistic regression analysis between the HCV genotypes and T2DM ($P = 1.000$). **Conclusion:** In the current study, we showed that patients with HCV infection are at a higher risk of developing T2DM, and T2DM showed to be a risk factor for the developing cirrhosis among patients with HCV infection.

INTRODUCTION

Hepatitis C is a multifactorial disease with different clinical and paraclinical features [1]. Some of these clinical manifestations are mixed cryoglobulinemia, porphyria cutanea tarda (PCT), and membranoproliferative glomerulonephritis [2-5]. Recently published articles suggest that diabetes mellitus type 2 (T2DM) is among the predisposing factors for the hepatitis C virus (HCV) infection [6]. The relationship between T2DM and HCV infection is not clarified yet, and other accompanying conditions such as aging, obesity, and other medical conditions cast doubt on this relationship [7]. T2DM is a complex multisystem disease mainly defined by several pathophysiological features,

including 1) a defect in insulin secretion, 2) increased hepatic glucose production, and 3) resistance to the action of insulin. The mechanism connecting these three features is still unknown [8].

Some studies have shown that HCV infection is a risk factor for T2DM [9-11]. The association between HCV infection and diabetes was first indicated in 1994 (5). Cirrhosis is a prevalent consequence of HCV infection, which also increases the risk of developing T2DM as well [12, 13]. Most studies investigating the relationship between T2DM and HCV infection are retrospective and cannot exclude confounding factors; for example, they lack adequate HCV genotype analysis. Besides, there is

no categorization of disease severity and cirrhosis in these studies, and there is an inadequate level of evidence to make confident conclusions. Knobler et al. (2000) showed that DM was more prevalent among biopsy-proven HCV-infected patients without cirrhosis and reported that T2DM was more prevalent in non-cirrhotic HCV patients (33%) compared to patients with no liver disease (5.6%) [14].

Considering the significance of HCV infection and T2DM for the health care systems and their related costs, there is an increasing need to investigate the possible association between these two medical conditions. This study investigated the association between HCV subtypes and cirrhosis status among diabetic and non-diabetic patients with HCV infection.

MATERIALS AND METHODS

Study design. This descriptive-analytical cross-sectional study was performed from Jan. 2017 to Jan. 2018 at Sina Clinical-Educational infectious diseases ward, the reference center for infectious diseases in northwest Iran. All patients with a positive HCV serology test and no previous history of T2DM were included in the survey, summing up to 48 included patients. The study was performed in compliance with the Helsinki declaration, and the Ethics Committee of Tabriz University of Medical Sciences approved the protocols (Code No. IR.TBZMED.REC.1396.729). The participants signed an informed written consent form that allowed us to use the current study data.

Study Population. The study included 18 to 75 years old serology-positive HCV patients with or without cirrhosis. The patients with hepatic cancer under interferon regimen, chronic renal diseases, hepatitis B virus infection, or systemic inflammatory disorders such as collagen vascular diseases and pregnant women were excluded from the study. By the end of the study, 48 patients were included, 19 of whom had a positive history of diabetes.

Data collection. A checklist was used to gather patients' information, including the demographic data (age, gender, height, weight, body mass index (BMI) and medical history), HCV genotype, complete blood count (CBC), fasting blood sugar (FBS), hemoglobin A1C (HbA1C), liver function tests, lipid profile, serum albumin, coagulation profile, and creatinine. The cirrhosis in patients was identified by ultrasonographic and radiologic findings or hepatic biopsy report.

Blood analysis. Five ML of blood was obtained from patients in heparinized Eppendorf tubes and sent to the Central Laboratory, Tabriz University of Medical Sciences. The blood analysis included CBC, FBS, HbA1C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, serum albumin, low-density lipoprotein (LDL), high-density lipoprotein

(HDL), triglyceride (TG), cholesterol (Chol), partial thromboplastin time (PTT), and creatinine (Cr). The same blood samples were used for the HCV serology test using ELISA and HCV genotyping using PCR.

HCV detection and genotyping. The Anti-HCV antibody was detected by a third-generation HCV ELISA (ELISA HCV 3.0 system [Ortho-Clinical Diagnostics, Test System Enhanced Save]). The ELISA HCV 3.0 uses microwells coated with a combination of recombinant HCV-encoded antigens originating from four regions of the viral genome. Also, for HCV genotyping real-time PCR was used. The real-time PCR benefited from specific probes for the subtypes 1a and 1b (NS5B region), genotypes 1, 2, 3, 4, 5, and 6 (5' NC region), and a probe for all genotypes (HCV-All probe) [15, 16].

Statistical Analysis. Descriptive statistical methods were used for reporting the groups, and data were expressed as mean \pm standard deviation (SD) or frequency and percentage (%). First of all, to compare the differences between diabetic and non-diabetic patients with HCV infection, the Chi-square test was used for dichotomous variables and an independent t-test for continuous variables. In case the data was not normal in distribution, the Mann-Whitney U test was used. Logistic regression analysis was performed to determine the association between the HCV genotypes and T2DM. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 16.0 (SPSS Inc., Chicago, IL). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Our study included 48 HCV-positive patients. Of these patients, 19 patients (39.5%) had T2DM, and eight (16.6%) had cirrhosis. Table 1 shows the demographics of patients categorized based on T2DM status. The patients' age ranged from 24 to 61 years old. The mean BMI was 19.30 ± 1.31 for diabetic, and 21.67 ± 2.14 for non-diabetic patients. The mean HCV infection course was 8.91 ± 2.18 years; this period for diabetic and non-diabetic patients was 9.03 ± 0.76 and 8.53 ± 1.01 years, respectively (*P* = 0.04). The relative risk for HCV-infected patients to develop cirrhosis with T2DM was 4.57 (95% CI :1.02-20.36, *P* = 0.04).

Laboratory findings. Red blood cell count, white blood cell count, platelet count, fasting blood sugar, hemoglobin A1C, aspartate transferase, alanine transferase, serum albumin, low-density lipoprotein, high-density lipoprotein, triglyceride, direct bilirubin, partial prothrombin time, and creatinine levels were evaluated among the recruited patients. The difference in laboratory findings in most of the parameters was not statistically significant, except for FBS and HbA1C, Serum Albumin, and PTT (Table 2).

Table 1. Demographic characteristics of patients categorized based on diabetes type 2 status (N = 48).

Variables	Diabetic N = 19	Non-diabetic N = 29	P-value
	Mean \pm SD	Mean \pm SD	
Age (year)	48.2 \pm 5.9	47.0 \pm 6.1	0.507
Weight (kg)	62.3 \pm 8.3	62.6 \pm 9.1	0.887
Height (cm)	169.3 \pm 8.3	167.6 \pm 9.1	0.534
	n (%)	n (%)	
Gender			
Male	11 (22.9)	7 (14.6)	0.039
Female	8 (16.6)	22 (45.9)	
Smoking	5 (26.3)	13 (44.8)	0.321
Alcohol consumption	8 (14.8)	5 (9.2)	0.095
Cirrhosis	6 (31.5)	2 (6.8)	0.044

SD, standard deviation; BMI, body mass index

Table 2. Laboratory findings among included patients with HCV infection (N = 48).

Variables	Diabetic (n = 19)	Non-diabetic (n = 29)	P-value
RBC ($\times 10^6/\mu\text{l}$)	4.8 \pm 0.9	4.7 \pm 0.1	0.602
WBC ($\times 10^3/\mu\text{l}$)	9.5 \pm 1.6	9.2 \pm 0.1	0.358
Platelet ($\times 10^3/\mu\text{l}$)	130.7 \pm 19.1	127.4 \pm 22.9	0.598
FBS (mg/dl)	125.2 \pm 20.3	84.9 \pm 15.3	< 0.001
HbA1C (percent)	7.3 \pm 1.8	6.3 \pm 0.3	< 0.001
AST (U/L)	76.8 \pm 11.9	72.5 \pm 11.6	0.221
ALT (U/L)	84.2 \pm 13.3	83.4 \pm 13.1	0.826
Serum Albumin (gr/L)	1.1 \pm 0.3	1.4 \pm 0.5	0.019
LDL (mg/dl)	197.6 \pm 42.1	197.0 \pm 32.7	0.959
HDL (mg/dl)	30.8 \pm 9.9	32.0 \pm 4.6	0.567
TG (mg/dl)	212.1 \pm 15.2	216.7 \pm 13.7	0.283
Direct bilirubin (mg/dl)	1.02 \pm 2.1	0.9 \pm 0.08	0.786
PTT (seconds)	14.2 \pm 2.1	16.5 \pm 1.6	< 0.001
Creatinine (mg/dl)	1.2 \pm 0.2	1. \pm 0.7	0.555

ALT, alanine transferase; AST, aspartate transferase, FBS; fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTT, partial prothrombin time; RBC, red blood cells; TG, triglyceride; WBC, white blood cells.

HCV Genotypes. Based on the PCR findings, 23 HCV patients (47.9%) had infections with genotype 1, 14 (29.2%) with genotype 2, 10 (20.8%) with genotype 3, and one (2.1%) with genotype 4. Table 3 shows the frequency of different HCV genotypes categorized based on T2DM. HCV type 1 was the most prevalent genotype among both diabetic and non-diabetic groups. Logistic regression analysis revealed no significant association between the HCV genotypes and the development of T2DM (P -value = 1.000).

DISCUSSION

The current study indicated that a high percentage of patients with HCV infection might develop T2DM. Also, patients with HCV infection and T2DM are more prone to develop cirrhosis than those only with HCV infection. Meanwhile, demographic features, laboratory findings, and HCV genotypes were not significantly different

between HCV-positive patients with and without T2DM. Patients with a more extended HCV period of infection were more prone to developing T2DM. Both T2DM and HCV infection are health issues imposing a heavy financial burden on health care systems worldwide.

Furthermore, since the first detection of HCV, an association of this infection with T2DM has given rise to the underlying mechanism linking these health conditions [17]. Most of the studies investigating the relationship between T2DM and HCV infection have found an increased T2DM frequency among those with HCV infection [18-20]. In contrast, some studies have ruled out the association between T2DM and HCV infection [21]. Accordingly, many studies have investigated the link between these two medical conditions. However, due to the diversity in their conclusions, it is not possible to come up with a robust and confident conclusion.

Table 3. Categorizing Hepatitis C virus genotyping based on diabetes status (N = 48).

HCV Genotype	Diabetic	Non-diabetic
	n (%)	n (%)
Type 1	10 (52.6)	13 (44.8)
Type 2	6 (31.5)	8 (27.6)
Type 3	2 (10.5)	8 (27.6)
Type 4	1 (5.4)	0
Total	19	29

Lin et al. (2000) investigated the possible relationship between T2DM and HCV infection and concluded that patients with HCV infection are at a higher risk of developing T2DM (17). The mean prevalence of T2DM in different populations is around 6.4% [22], but in the current study, the prevalence of T2DM among HCV patients was 39.58%, although the HCV patients' population was too small to reach a definite conclusion. The relationship between T2DM and cirrhosis was significant in our study (P -value = 0.04), which agrees with previous studies. In a study by Antonelli et al. (2005) on the association between HCV infection and DM1 and T2DM, the patients with HCV infection and T2DM were at a higher risk of developing cirrhosis and hepatocellular carcinoma [23], which is in agreement with our findings. Interestingly, HCV treatment protocols have exhibited a positive effect on diminishing T2DM features [24]. Another study conducted in southern Iran reported a high prevalence of HCV infection among diabetic patients, supporting the current study's findings [25].

In similar studies in the United States and Egypt, no association between T2DM and HCV infection was found [26, 27]. This finding contrasts our results that showed no statistically significant relationship between liver function tests in individuals with and without T2DM.

In the current study, T2DM proved to be a risk factor associated with cirrhosis in HCV patients; T2DM as a risk factor for cirrhosis in other health conditions such as metabolic syndrome, cryptogenic cirrhosis, and non-alcoholic steatohepatitis was already proven [28-32]. The primary pathophysiologic process proposed to intervene in this relationship between T2DM and cirrhosis is that T2DM accelerates hepatocyte destruction, leading to increased liver function tests [33]. However, the liver function tests in the current study between groups with and without T2DM were not statistically different.

There was a significant association among the genders in this study (P -value = 0.039), which suggests that the chance of being diabetic is more among the males, which was also evident in previous studies [34]. A statistically significant difference was observed in the current study

between the laboratory levels of fasting blood sugar, hemoglobin A1C, serum albumin, and partial prothrombin time in the two groups. These differences can be explained through the impact of HCV, which, as a liver infection, impairs the protein synthesis function in the liver and results in changes in the levels of albumin and coagulation proteins [35]. Also, higher fasting blood sugar and hemoglobin A1C, as the primary laboratory representatives of diabetes, are explainable in the diabetic group [36].

In a study by Mason et al. (1999) on the association of different HCV genotypes with T2DM, HCV infection not only aggravated other disorders and T2DM as well. Among all HCV genotypes, genotype 2 was of a higher possibility to result in T2DM development [37]. Our study showed a significant association between T2DM and HCV infection; however, no significant association was seen between the HCV genotypes and diabetes, which could be due to the low sample size.

A chief limitation in the current study was the low number of HCV patients, which did not allow us to make a more confident conclusion. Another factor that might cast doubt on our conclusion was how cirrhosis was defined because cirrhosis was reported based on the previous radiographic findings or biopsy findings. A precise description of tissue features could have enriched the current study by further investigating this pathologic feature.

We demonstrated that patients with HCV infection are at a higher risk of developing T2DM. We also showed that an extended infection period increased the probability of T2DM development. The T2DM proved to be a risk factor for cirrhosis development among patients with HCV infection. Further studies with bigger sample sizes and considering other possible confounding factors will increase our insight into the probable underlying link between T2DM and HCV infection.

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