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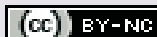
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Clinical features of patients with type 2 diabetes mellitus and hepatitis C infection

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Abstract

The objective of the present cross-sectional study was to assess the prevalence and the clinical and laboratory features of hepatitis C virus (HCV)-positive patients with type 2 diabetes mellitus (DM) attending either an outpatient clinic or hemodialysis units. Serologic-HCV testing was performed in 489 type 2 DM patients (303 outpatients and 186 on dialysis). A structured assessment of clinical, laboratory and DM-related complications was performed and the patients were then compared according to HCV infection status. Mean patient age was 60 years; HCV positivity (HCV+) was observed in 39 of 303 (12.9%) outpatients and in 34 of 186 (18.7%) dialysis patients. Among HCV+ patients, 32 were men (43.8%). HCV+ patients had higher serum levels of aspartate aminotransferase (0.90 ± 0.83 vs 0.35 ± 0.13 μ Kat/L), alanine aminotransferase (0.88 ± 0.93 vs 0.38 ± 0.19 μ Kat/L), gamma-glutamyl transferase (1.57 ± 2.52 vs 0.62 ± 0.87 μ Kat/L; $P < 0.001$), and serum iron (17.65 ± 6.68 vs 14.96 ± 4.72 μ M; $P = 0.011$), and lower leukocyte and platelet counts ($P = 0.010$ and $P < 0.001$, respectively) than HCV-negative (HCV-) patients. HCV+ dialysis patients had higher diastolic blood pressure than HCV- patients (87.5 ± 6.7 vs 81.5 ± 6.0 mmHg; $P = 0.005$) and a lower prevalence of diabetic retinopathy (75 vs 92.7%; $P = 0.007$). In conclusion, our study showed that HCV is common among subjects with type 2 DM but is not associated with a higher prevalence of chronic diabetic complications.

Key words: Type 2 diabetes; Hepatitis C; Dialysis

Introduction

Type 2 diabetes mellitus (DM) is a prevalent disease that affects 7.6% of the Brazilian population (1). It is linked to several chronic complications such as retinopathy, nephropathy, peripheral, and autonomic neuropathy, as well as to a high prevalence of cardiovascular disease (2).

Hepatitis C virus (HCV) infection is also a common disease worldwide, and its prevalence varies according to population, ranging from 0.6% among volunteer blood donors to 80% among intravenous drug users, with an estimated overall prevalence of 3% (3).

Since 1994, several groups have reported an association between HCV infection and type 2 DM (4-13). The prevalence of HCV infection among diabetic subjects ranges from 2 to 11.5% (12-14) and seems to be unrelated to hepatic fibrosis grade or to the presence of cirrhosis. HCV infection appears to precede the development of type 2 DM (10). Inflammatory cytokines such as tumor necrosis factor- α (TNF- α), soluble TNF receptor 1 (sTNFR1), sTNFR2 and interleukin-6 (15), serum levels of ferritin (16), and adi-

ponectin, an anti-inflammatory cytokine (17,18), may be involved in its pathogenesis.

The presence of HCV infection in patients with DM may also increase the proportion of DM-related chronic complications. In fact, there are some reports showing that HCV infection is associated with an increased risk of developing diabetic nephropathy (18). Moreover, end-stage renal disease patients with type 2 DM and positive HCV infection (HCV+) undergoing renal replacement therapy have a worse cumulative survival. However, these studies were conducted on selected populations of Afro-American (19) and Afro-Caribbean (20) patients, which may have influenced the results.

In view of these considerations, the objective of the present study was to analyze the frequency of HCV infection in a cohort of type 2 DM patients attending an outpatient clinic of a general hospital or dialysis units and to evaluate the clinical and laboratory features associated with HCV infection in these patients.

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Patients and Methods

Patients

A cross-sectional study was conducted on 303 consecutive patients with type 2 DM attending the outpatient clinic of the Hospital de Clínicas de Porto Alegre from December 2005 to December 2007. We also analyzed 186 patients with type 2 DM from 3 hemodialysis units in Porto Alegre and surrounding areas. Type 2 DM was defined as disease onset after 30 years of age, no previous episode of ketoacidosis or documented ketonuria, and treatment with insulin only 5 years after diagnosis.

Hospital de Clínicas de Porto Alegre's Ethics Committee approved this study, and written informed consent was obtained from all patients.

Patient evaluation

Patients underwent a standardized evaluation consisting of a questionnaire, physical examination, and laboratory tests. Weight and height were measured in patients without shoes and wearing light outdoor clothing and body mass index (BMI) was calculated [weight (kg)/height(m)²]. Waist circumference at the narrowest point as viewed from the front and hip circumference at the widest point was also measured. Blood pressure (BP) was measured according to JNC 7 recommendations (21) in the left arm of the patient in a sitting position, after a 5-min rest and using a mercury sphygmomanometer. The average of two office BP measurements was used for analysis. Hypertension was defined as systolic BP (SBP) \geq 140 mmHg and/or diastolic BP (DBP) \geq 90 mmHg on at least 2 occasions, or when the subject was using antihypertensive medication(s).

Urinary albumin excretion (UAE) was measured using two collection methods, according to their availability at the center: a 24-h timed urine collection or random spot sterile urine samples. The cutoff values used to define the stages of renal involvement followed the recommendations of the American Diabetes Association for timed urine collection. Subjects were classified as having normoalbuminuria if albumin in the collection was less than 20 μ g/min, microalbuminuria if the levels of albumin in the collection were greater than 20 μ g/min but smaller than 200 μ g/min, and macroalbuminuria if the levels were greater than 200 μ g/min. For spot samples, urine concentration (mg/L) cutoffs were used as previously validated in our central laboratory (22) as follows: normoalbuminuria (<17 mg/L), microalbuminuria (17-174 mg/L), and proteinuria (>174 mg/L).

An ophthalmologist performed direct funduscopy, and diabetic retinopathy was classified as absent, nonproliferative or proliferative.

Coronary heart disease (CHD) was diagnosed as previously described (23). Briefly, CHD was established in the presence of angina or possible infarct according to the World Health Organization Cardiovascular Questionnaire and/or the presence of resting electrocardiogram abnor-

malities (Minnesota Code Q and QS patterns [1.1-2, 1.3]; S-T junction [J] and segment depression [4.1-4]; T wave items [5.1-3], and complete left bundle block [7.1]) and/or the presence of perfusion abnormalities (fixed or variable) upon myocardial scintigraphy at rest and after dipyridamole administration. Intermittent claudication (WHO Cardiovascular Questionnaire (24)) and/or absence of a posterior tibial pulse upon clinical examination indicated peripheral vascular disease (PVD). Cerebrovascular disease was established on the basis of a history of stroke and/or presence of compatible findings.

Distal sensory neuropathy (DSN) was diagnosed based on the presence of typical symptoms or abnormal results in a 10-g Semmes-Weinstein monofilament sensory perception test at the hallux of each foot.

Information about HCV status was based on anti-HCV test, polymerase chain reaction (PCR) for HCV or hepatic biopsy and information about treatment was obtained from medical chart data, when available. If patients were positive in the anti-HCV test, they were evaluated by PCR for HCV. Given the small availability of the test during the study, most patients did not have data about genotype or viral load by the end of the study.

Data for dialysis patients were obtained only through medical chart review. Ultrasonography was not available for any patient at the time of the study.

Laboratory methods

Serological testing for anti-HCV and hepatitis B surface antigen (HBsAg) was done using a second-generation enzyme immunoassay (DiaSorin[®], Italy). The anti-HCV test has a sensitivity of 100% and a diagnostic specificity of 99.8%. PCR for HCV was performed by Immunoblot (RIBA, USA). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by the UV kinetic method (Roche[®] Diagnostics, USA), and gamma-glutamyl transferase (GGT) was determined by a kinetic colorimetric method (HITACHI 911 Analyzer, Germany).

UAE was measured by immunoturbidimetry (Microalb, Ames Bayer[®], USA; intra- and interassay coefficient variations of 4.5 and 11.0%, respectively). Hemoglobin A1c was measured by HPLC (Merck-Hitachi 9100[®], Germany; normal range 4-6%) and fasting plasma glucose by the glucose-peroxidase colorimetric enzymatic method (Biodiagnóstica[®], Colombia). Creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method. Sedimentation rate was measured by a kinetic and photometric automated method, and C-reactive protein (CRP) by nephelometry (Behring, Canada).

A complete blood count was obtained by light absorbance, impedance and flow cytometry. Serum iron, transferrin saturation and ferropexic capacity were measured by the ferrozin colorimetric method (Roche[®] Diagnostics, Germany) and ferritin was measured by chemiluminescence (IMMULITE[®] 2000, USA).

Statistical analysis

The Student *t*-test or chi-square test was used to compare clinical and laboratory data. Quantitative variables not in a normal distribution were log transformed. A *P* value of 0.05 was considered to be significant.

Results

Prevalence

Anti-HCV testing was positive in 73 of 489 patients (15%) - 39 of 303 (12.9%) outpatients and 34 of 186 (18.27%) dialysis patients. Of the total 73 patients with both diabetes and positive HCV testing, 46 were newly diagnosed by the screening method and 27 had already been diagnosed. Of these, 3 had eliminated the virus spontaneously and 6 had been treated with interferon + ribavirin (only 1 eliminated the virus).

The main risk factor for HCV was blood transfusion before 1992 (16 patients), and no risk factor was identified in the remaining patients. Among the patients with an identifiable risk factor, possible HCV exposure had occurred on average 14.3 years before the diagnosis of DM. However, 4 of 23 patients had received a diagnosis of DM an average of 11.6 years before the possible exposure to HCV.

Six of the patients had been clinically diagnosed with cirrhosis (all of them were in Child's A stage), but only 4 patients had data about a liver biopsy in their medical chart.

Outpatients

Clinical and laboratory features. Clinical and laboratory features are shown in Table 1. There was no difference between HCV+ and HCV-negative (HCV-) patients concerning age, age at diagnosis of DM, duration of DM, ethnicity, gender distribution, smoking status, family history of DM, or proportion with diagnosis of hypertension. SBP and DBP, BMI, waist circumference, glycemic control (fasting plasma glucose and A1c test), and lipid profile were also similar for the two groups. The use of statins and of an angiotensin-converting enzyme inhibitor (ACEI) was higher in the HCV- than in HCV+ group, while the use of fibrates did not differ between groups. As expected, liver function tests (ALT, AST, and GGT) were higher in HCV+

than in HCV- patients. Among patients with abnormal liver tests (>2.5 x above the upper limit of normal, ULN) 40% were HCV+, whereas only 11.2% of the patients with normal liver tests (≤ 2.5 x ULN) were HCV+. The presence of abnormal liver tests is predictive of HCV infection, with an odds ratio of 5.31 (95%CI = 2.29-12.30). In addition, 8.3% of the patients without viral hepatitis (HCV- and HBsAg-) had abnormal liver tests (Table 2).

Platelet and leukocyte counts were lower in HCV+ patients, while serum iron was higher. Ferritin tended to be higher, but the difference was not statistically significant. Hematocrit, total hemoglobin, ferropexic capacity, and transferrin saturation were similar for the two groups. Inflammatory markers such as CRP and sedimentation rate did not differ between groups (Table 2).

Chronic complications of diabetes. Diabetic retinopathy was present in 102 (51.5%) of the HCV- and in 12 (35.3%) of the HCV+ patients (*P* = 0.27; Table 3). Analysis of the severity of retinopathy (nonproliferative or proliferative) did not show any difference between HCV+ and HCV- patients (*P* = 0.39).

Diabetic nephropathy was present in 52.7% of HCV- and in 48.8% of HCV+ patients (*P* = 0.640). The proportion of subjects with microalbuminuria or macroalbuminuria was

Table 1. Clinical features of type 2 diabetes mellitus outpatients and dialysis patients who were HCV- or HCV+.

	Outpatients		Dialysis patients	
	HCV- (N = 226)	HCV+ (N = 39)	HCV- (N = 132)	HCV+ (N = 34)
Age (years)	58.8 ± 10.0	61.0 ± 11.5	61.3 ± 10.4	58.9 ± 10.4
Women	122 (53.9)	24 (61.5)	56 (42.4)	17 (50)
White	160 (70.8)	29 (74.3)	79 (59.8)	19 (55.9)
BMI (kg/m ²)	30.2 ± 5.2	30.0 ± 5.3	25.8 ± 6.0	24.6 ± 5.3
DM duration (years)	12.6 ± 8.3	12.0 ± 9.0	19.5 ± 9.7	18.0 ± 10.5
Hypertension ⁺	104 (90.4)	33 (84.6)	34 (94.4)	9 (100)
SBP (mmHg) ⁺⁺	141 ± 24.5	138 ± 20.3	146.5 ± 16	156 ± 14
DBP (mmHg) ⁺⁺	84 ± 14.5	84 ± 11.4	81.5 ± 6.0	87.5 ± 6.7*
Smoking				
Current	35 (15.5)	2 (5.1)	9 (6.8)	2 (5.9)
Ex	73 (32.3)	16 (41.0)	55 (41.6)	19 (55.9)
Family history				
Mother	92 (40.7)	19 (48.7)	48 (36.7)	13 (38.2)
Father	45 (19.9)	7 (17.9)	30 (22.7)	8 (23.5)
Statin use ⁺⁺⁺	107 (47.4)	7 (19.4) [#]	17 (23.3)	7 (29.2)
Fibrate use	15 (6.6)	0 (0)	1 (0.8)	0 (0)
ACEI use	124 (54.9)	14 (35.9)	67 (50.8)	17 (50)

Data are reported as means ± SD or number (%) of patients. BMI = body mass index; DM = diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; ACEI = angiotensin-converting enzyme inhibitor. **N* = 115 for HCV- outpatients; *N* = 45 for dialysis patients (36 HCV- and 9 HCV+); ***N* = 58 for dialysis patients (47 HCV- and 11 HCV+); ****N* = 97 for dialysis patients (73 HCV- and 24 HCV+). **P* < 0.05 compared to HCV- (Student *t*-test). #*P* < 0.05 compared to HCV- (chi-square test).

Table 2. Laboratory features of type 2 diabetes mellitus outpatients and dialysis patients who were HCV- or HCV+.

	Outpatients		Dialysis patients	
	HCV- (N = 250)	HCV+ (N = 39)	HCV- (N = 140)	HCV+ (N = 34)
Fasting glucose (mM)	9.39 ± 3.94	8.78 ± 3.11	9.92 ± 5.28	9.16 ± 4.22
A1c test (%)	8.0 ± 1.9	8.0 ± 2.1	6.3 ± 2.5	7.0 ± 2.6
Total cholesterol (mM)	4.78 ± 1.14	4.47 ± 1.28	4.45 ± 1.01	4.63 ± 1.60
HDL cholesterol (mM)	1.29 ± 0.36	1.37 ± 0.41	1.11 ± 0.44	1.14 ± 0.62
LDL cholesterol (mM)	2.61 ± 0.98	2.43 ± 1.08	2.38 ± 0.93	2.40 ± 1.39
Triglycerides (mM)	1.67 (0.30-18.84)	1.13 (0.47-3.79)	1.87 (0.61-9.90)	1.96 (0.55-5.68)
Serum creatinine (μM)	114.92 ± 141.44	114.92 ± 167.96	663.00 ± 247.52	698.36 ± 221.00
AST (GOT) (μKat/L)	0.35 ± 0.13	0.90 ± 0.83*	-	-
ALT (GPT) (μKat/L)	0.38 ± 0.19	0.88 ± 0.93*	-	-
GGT (μKat/L)	0.62 ± 0.87	1.57 ± 2.52*	-	-
Hematocrit (%)	39.4 ± 4.5	39.1 ± 5.5	32.2 ± 7.1	32.5 ± 5.8
Hemoglobin level (g/L)	130 ± 24	128 ± 20	109 ± 23	112 ± 17
Leukocytes (cells/μL)	7831 ± 3987	6146 ± 2132*	-	-
Platelets (U/μL)	244550 ± 66347	171482 ± 68187*	-	-
Serum iron (μM) ⁺	14.96 ± 4.72	17.65 ± 6.68*	-	-
Ferritin (μg/L) ⁺	213.9 ± 182	287 ± 316	-	-
Ferropexic capacity (μM) ⁺	58.87 ± 14.00	62.01 ± 9.65	-	-
Transferrin saturation (%) ⁺	26.3 ± 9.3	29.5 ± 12.0	-	-
C-reactive protein (mg/L) ⁺	5.8 ± 11.2	3.6 ± 5.0	-	-
Sedimentation rate (mm/h) ⁺	19.8 ± 18.3	20.8 ± 18.5	-	-

Data are reported as means ± SD. Triglyceride levels are reported as median (range). A1c test = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; AST = aspartate aminotransferase (GOT = glutamic-oxaloacetic transaminase); ALT = alanine aminotransferase (GPT = glutamic-pyruvic transaminase); GGT = gamma-glutamyl transferase. *N = 215 for HCV- and 39 for HCV+ outpatients. *P < 0.05 compared to HCV- (Student *t*-test).

Table 3. Chronic complications of type 2 diabetes mellitus outpatients and dialysis patients who were HCV- or HCV+.

	Outpatients		Dialysis patients	
	HCV- (N = 198)	HCV+ (N = 34)	HCV- (N = 124)	HCV+ (N = 29)
Diabetic retinopathy (Yes)	102 (51.5)	12 (35.3)	115 (92.7)	22 (75.9)*
Nonproliferative	49 (24.7)	10 (28.6)	42 (33.9)	7 (24.1)
Proliferative	52 (26.3)	5 (14.3)	70 (56.5)	16 (55.2)
Nephropathy (Yes) ⁺	136 (52.7)	16 (48.8)		
Microalbuminuria ⁺	82 (31.8)	11 (32.5)		
Macroalbuminuria ⁺	28 (10.9)	4 (10)		
Dialysis ⁺	26 (10.1)	3 (7.5)		
Distal sensory neuropathy (Yes) ⁺⁺	45 (22.5)	10 (31)	33 (51.6)	8 (44.4)
Peripheral vascular disease (Yes)	48 (24.2)	30 (87.5)	59 (47.4)	11 (37)
Coronary heart disease (Yes)	83 (41.9)	14 (41.7)	89 (72)	17 (58.3)
Cerebrovascular disease (Yes)	19 (9.5)	3 (9.7)	16 (13)	2 (6.1)

Data are reported as number (%) of patients. *N = 258 for HCV- and 34 for HCV+ outpatients; **N = 82 for dialysis patients (64 HCV- and 18 HCV+). *P < 0.05 compared to HCV- (chi-square test).

also similar for the two groups.

The prevalence of DSN, PVD, CHD, and cerebrovascular disease was similar in both groups (Table 3).

Patients on dialysis

Clinical and laboratory features. The clinical and laboratory features of these patients are shown in Table 2. There was no difference between HCV+ and HCV- patients regarding age, age at diagnosis of DM, duration of DM, ethnicity, gender distribution, smoking status, family history of DM, or diagnosis of hypertension. SBP, BMI, waist circumference, glycemic control (fasting plasma glucose and A1c test) and lipid profile were also similar for the two groups. The use of statins, fibrates and ACEI did not differ between the HCV- and HCV+ groups, although no HCV+ patients were using fibrates. DBP was significantly higher in the HCV+ group than in the HCV- group. Hematocrit and hemoglobin levels were similar for the two groups.

Chronic complications of diabetes. The prevalence of diabetic retinopathy was significantly higher in HCV- (92.7%) than in HCV+ (75.9%) patients, but the severity of retinopathy was similar (Table 3). The prevalence of DSN, PVD, CHD, and cerebrovascular disease was also similar in both groups, as shown in Table 3.

Discussion

The present study observed a higher frequency of HCV infection in patients with type 2 DM than would be expected amongst the general population (13,20,25), and HCV infection seemed to precede the development of DM, as the average time between possible exposure to HCV and DM diagnosis was 14.3 years. However, HCV+ DM patients did not present a higher prevalence of chronic complications of DM.

An increased prevalence of HCV infection has been reported by other investigators (12,13) and the rate observed in the present study (15%) is very similar to the 11.5% rate reported by Simo et al. (13) in a sample of white patients with type 1 and type 2 DM. The association of type 2 DM and HCV infection might be due to an increased susceptibility of type 2 DM patients to more frequent hospitalizations and daily use of syringes (10). Alternatively, HCV infection might predispose patients to the development of type 2 DM, by interfering in lipid metabolism, inhibiting signaling pathways in the liver, increasing hepatic steatosis and then inducing insulin resistance (5,15,26,27). However, the exact mechanism of insulin resistance induced by HCV remains to be clarified.

Our study did not confirm previous reports of a distinct DM phenotype associated with HCV infection (13,28-30), with HCV+ diabetic patients being leaner and presenting lower total and LDL cholesterol levels than HCV- diabetic patients. The finding that our patients had similar LDL and total cholesterol levels may be partially explained by the

more frequent use of statins by HCV- outpatients.

Family history was listed in some studies as a risk factor for the development of HCV-associated type 2 DM (29,31), but in our study, the presence of a family history of DM did not differ between groups.

The only clinical features in our study that might be helpful to identify HCV+ patients among diabetic patients were abnormal liver enzymes. Although we did not evaluate the presence of hepatic steatosis, which is part of metabolic syndrome, and therefore commonly found in diabetic patients, we think that screening for HCV infection should be done in all DM patients with abnormal liver enzymes, as done in the general population, since they are predictive of HCV infection. Abnormal liver tests in patients without viral hepatitis might be due to non-alcoholic steatohepatitis or other hepatopathies.

Inflammatory markers such as CRP, sedimentation rate and ferritin levels, that were also thought to be a clue for identifying HCV+ patients, were similar in our study, despite the idea of an inflammatory link between the two diseases. In further studies, other inflammatory markers, such as adipocytokines, should be assessed, as they seem to play a role in insulin resistance (32).

The presence of HCV infection does not seem to change the development of chronic complications of DM, since their prevalence were similar for HCV+ and HCV- patients. It was thought that HCV+ patients could have a higher prevalence of proteinuric nephropathy since the most frequent extrahepatic manifestation of HCV is mixed cryoglobulinemia (33). We did not measure serum cryoglobulins nor did we perform a renal biopsy since the prevalence of proteinuric nephropathy was the same in both HCV- and HCV+ patients. In fact, the prevalence of retinopathy was lower among HCV+ patients in the dialysis group. We speculate that this could be due to a survival bias since it has been reported that HCV+ patients with type 2 DM undergoing renal replacement therapy have a worse cumulative survival (19). Perhaps the less severe cases, which are the ones who survive, presented less retinopathy. In addition to the inability to perform a renal biopsy to assess the particular cause of nephropathy, another weakness of our study is that our patients did not have an ultrasonography available to help in the evaluation of liver damage. However, the main results of the study would not be altered if ultrasonography data were available because there were no significant clinical differences between groups.

Our findings confirm the hypothesis of a study performed in an Italian population (34), in which HCV+ did not worsen vascular complications in DM patients. That study discussed whether abnormalities induced by hepatopathy (lower cholesterol levels, lower platelet counting) could protect the cardiovascular system against atherosclerosis, while another Japanese study (35) found HCV antibodies to be an independent risk factor for atherosclerosis. In the present study, we did not assess atherosclerosis itself, but evaluated its clini-

cal outcomes (coronary artery disease and peripheral vascular disease), and their prevalence did not differ between HCV+ and HCV-, in either the outpatient or in dialysis group.

HCV infection was found to be more common in patients with type 2 DM than among the general population, and therefore, we suggest that these patients be regularly tested for HCV infection, especially those with abnormal liver tests. However, a cost-benefit study is necessary to assess the real gain for the patients. This approach is in agreement with the current literature. Gutiérrez-Grobe et al. (36) suggested, recently, that all patients with hepatitis C should be screened for type 2 diabetes given the increasing prevalence of both conditions worldwide and the pro-inflammatory state, which

links both conditions (15-18,37,38).

In our study, the presence of HCV infection was not associated with a higher prevalence of chronic complications of DM. A prospective study would be important to evaluate if the presence of HCV would predispose to the development of chronic complications and influence the mortality rate and cause of death.

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