ORIGINAL ARTICLE

C-reactive protein and chronic hepatitis C virus infection in diabetic patients

Marcin Skowroński[1,3], Dorota Zozulińska-Ziółkiewicz[1], Jacek Juszczyk[2], Wojciech Michalski[4], Bogna Wierusz-Wysocka[1]

1 Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznań, Poland
2 Department of Infectious Diseases, Poznan University of Medical Sciences, Poznań, Poland
3 Wielkopolska Center of Pulmonology and Thoracosurgery of Janusz and Eugenia Zeyland, Poznań, Poland
4 Clinical Trials Office and Biostatistics Unit, Marie Skłodowska-Curie Institute of Oncology, Warszawa, Poland

KEY WORDS

diabetes, hepatitis C virus, inflammatory markers

ABSTRACT

INTRODUCTION C-reactive protein (CRP) is one of the most widely used risk markers of cardiovascular disease in clinical practice. The contribution of hepatitis C virus (HCV) infection to low-grade inflammation in diabetic patients and its significance for cardiovascular risk scoring remain unclear.

OBJECTIVES The aim of the study was to investigate the relationship between HCV infection and CRP levels as one of the markers of cardiovascular risk in diabetic patients.

PATIENTS AND METHODS We compared patients with HCV infection and diabetes (n = 46) with HCV-negative type 1 (n = 56) or type 2 diabetic patients (n = 54), as well as HCV patients without diabetes (n = 54).

RESULTS CRP levels in diabetic HCV patients were lower than in type 2 diabetic patients ($P < 0.001$), similar to those in the type 1 diabetic group ($P = 0.747$), and higher than in nondiabetic HCV subjects ($P = 0.002$). The median values were 1.07, 2.58, 0.91, and 0.45 mg/l, respectively. White blood cell count in diabetic HCV subjects was lower than in those with type 2 diabetes ($P = 0.029$) and similar to that found in type 1 diabetic ($P = 0.064$) and nondiabetic HCV patients ($P = 0.279$). There was difference in erythrocyte sedimentation rate between diabetic and nondiabetic HCV groups ($P = 0.025$); the respective medians were 10 and 5 mm/h.

CONCLUSIONS These findings indicate that HCV hepatitis may modulate chronic inflammatory state in diabetic patients. Moreover, these results suggest that screening for HCV should be considered prior to assessment of cardiovascular risk in diabetic patients, because the results may affect the cardiovascular risk scoring.

Correspondence to:
Marcin Skowroński, MD, PhD, Wielkopolskie Centrum Pulmonologii i Torakochirurgii im. Janusza i Eugenii Zeylandów, Szpital w Ludwikowie k/Poznania, 62-050 Mosina, Poland, phone: +48-61-813-28-31, fax: +48-61-813-28-79, e-mail: marcinas@gazeta.pl
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INTRODUCTION It is accepted that traditional risk factors for cardiovascular disease, such as hypertension, smoking, hypercholesterolemia, and diabetes, do not entirely explain the occurrence of cardiovascular events.[1] Apparently, only a half of patients with coronary heart disease have hyperlipidemia.[2] Therefore, C-reactive protein (CRP) as an inflammatory marker has been proposed as a nontraditional risk factor.[3] Moreover, there is firm evidence to support a theory that CRP is a strong predictor of cardiovascular events.[4] Similarly, both white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) have been associated with cardiovascular risk.[5,6]

CRP has been extensively studied in various groups of patients including both type 1 and 2 diabetic patients as well as individuals with metabolic syndrome.[7,8] It has been clearly demonstrated that CRP levels in patients with various glucose abnormalities are elevated as a result of chronic subclinical inflammation. Furthermore, it seems that an increase in CRP levels is correlated with cardiovascular risk in these groups.[9,10] However, there are far less data on the role of CRP in the growing group of patients with diabetes and HCV infection.

In the majority of studies, diabetes in HCV patients has been classified as type 2. Both insulin

TABLE 1 Clinical and laboratory characteristics of the study groups

Parameter	Patient groups			
	DM-HCV (n = 46)	T2DM (n = 54)	T1DM (n = 56)	Non-DM-HCV (n = 52)
men/women	25/21	30/24	30/26	34/18
age, y	48.9 (12.4)	51.2 (4.3)	48.6 (6.0)	47.0 (8.7)
BMI, kg/m^2	28.5 (4.9)	32.4 (4.7)[a,c]	24.0 (2.7)[a,b]	26.4 (3.7)
duration of diabetes, y	5.0 (1.8; 8.0)[b]	8.0 (5.0; 13)	12.5 (6.0; 25)[a,b]	–
duration of HCV infection, y	3.0 (0.5; 5.0)	–	–	3.0 (0.5; 8.0)
family history of diabetes, n (%)	25 (52.1)	26 (54.2)	15 (27.8)[a,b]	–
smoking, n (%)	14 (29.2)	17(32.1)	18 (32.7)	24 (46.2)
hypertension, n (%)	28 (56.0)[b]	46 (86.8)	32 (57.1)[b,c]	5 (9.6)[b]
insulin, n (%)	35 (70.0)[b]	14 (25.9)	56 (100)	–
metformin, n (%)	6 (12.0)[b]	33 (61.1)	–	–
sulfonylureas, n (%)	9	10	–	–
ACE inhibitors, n (%)	27 (54.0)	37 (68.5)	9 (16.1)	3 (5.8)
aspirin n (%)	4 (8.0)	28 (51.9)	31 (55.4)	3 (5.8)
statins n (%)	0	18 (33.3)	8 (14.3)	–
FPG, mmol/l	155 (55)	137 (32)	156 (38)[b,c]	88 (10)[a]
HbA_{1c}, %	8.0 (2.5)	8.3 (1.8)	8.7 (1.3)[a]	–
AST, IU/l	89.2 (58.6)[b]	22.9 (7.4)[c]	20.4 (5.5)[a,c]	66.1 (49.4)[a]
ALT, IU/l	120.5 (92.1)[b]	28.4 (9.7)[c]	20.6 (8.5)[a,b,c]	94.1 (70.1)
total cholesterol, mmol/l	4.3 (1.0)[b]	5.3 (1.4)	5.6 (1.0)[a]	4.5 (0.9)
LDL-C, mmol/l	2.5 (0.6)[b]	3.5 (0.9)	3.5 (1.0)[a]	2.7 (0.7)
HDL-C, mmol/l	1.1 (0.4)	1.1 (0.2)	1.6 (0.3)[a]	1.2 (0.3)
triglycerides, mmol/l	4.0 (2.6)[b]	5.8 (6.7)	3.0 (1.4)[a]	3.0 (1.2)

Data presented as means (SD) or median (25%; 75%)

a $P < 0.05$ vs. DM-HCV, **b** $P < 0.05$ vs. T2DM, **c** $P < 0.05$ vs. non-DM HCV

Abbreviations: ACE – angiotensin-converting enzyme, ALT – alanine aminotransferase, AST –- aspartate aminotransferase, BMI – body mass index, DM-HCV – diabetes mellitus-hepatitis C virus, HbA_{1c} – hemoglobin A_{1c}, FPG – fasting plasma glucose, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, T1DM – type 1 diabetes, T2DM – type 2 diabetes, SD – standard deviation

resistance and β-cell dysfunction contribute to glucose abnormalities in these patients.[10] However, there is evidence that HCV directly damages β-cells or disturbs their function.[11] Therefore, it seems that diabetes in HCV patients has unique and complex pathogenesis which distinguishes this metabolic disorder from type 2 diabetes.

The aim of our study was to analyze CRP, WBC, and ESR in diabetic patients with chronic HCV infection.

PATIENTS AND METHODS From January 2007 to September 2009, we recruited 46 consecutive white diabetic patients with HCV (DM-HCV) (25 men, 21 women; aged 48.9 ±12.4 years), admitted to the Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poland. The majority of diabetic anti-HCV-positive patients were referred either from the Infectious Diseases Department or from the Outpatient Liver Unit (both Poznan University of Medical Sciences). The second group consisted of 52 HCV patients without diabetes or impaired glucose tolerance (non-DM-HCV) (34 men, 18 women; aged 47.0 ±8.7 years). HCV patients were included if they fulfilled the following criteria: positive anti-HCV (HCV 3.0 ELISA Test System with Enhanced SAVe; Ortho-Clinical Diagnostics, Bucks, United Kingdom) and HCV RNA by polymer chain reaction (COBAS AmpliScreen HCV Test. 2.0; Roche Molecular Systems, Branchburg, New Jersey, United States) (sensitivity 100 IU/ml against the World Health Organization International Standard). A percutaneous liver biopsy was performed, if informed consent was obtained, in 39 diabetic HCV and 39 nondiabetic HCV patients. Liver fibrosis was assessed and staged according to the method by Scheuer.[13] The estimated duration of the infection was defined as the time from detection of positive serological markers of the HCV infection. Patients with hepatitis B virus (HBV) (HBsAg or HBV-DNA-positive), autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease or liver disease of different etiology (hepatotoxic drugs or alcohol abuse) and with chronic kidney disease (creatinine >124 μmol/l) were excluded. We also excluded patients who had clinical evidence of cirrhosis and

chronic inflammatory diseases and patients with anemia (men and women with hemoglobin levels of 7.4 and 6.8 mmol/l, respectively), leucopenia (WBC count <4 G/l), and those treated with steroid or nonsteroidal anti-inflammatory drugs, except aspirin. Two additional groups were evaluated: 54 patients with type 2 diabetes (T2DM) (24 women, 30 men, aged 51.2 ±4.3 years) and 56 patients with type 1 diabetes (T1DM) (26 women, 30 men, aged 48.6 ±6.0 years). We decided to include type 1 and 2 diabetic patients due to unique and multifactorial pathogenesis of diabetes in patients with HCV infection. Patients with newly diagnosed type 1 diabetes (<1 year) were excluded. Both diabetic groups had normal liver function tests, no serologic evidence of HCV or HBV infection, and no recent acute illness.

The study protocol had been approved by the local Ethics Committee in Poznań, Poland. Informed consent was obtained from all participants.

A family history of diabetes was defined as the presence of diabetes in either 1 parent or 1 first- or second-degree relative. The body mass index (BMI) was calculated as weight (kg)/height (m^2).

Glycated hemoglobin (HbA_{1c}) was measured using high-performance liquid chromatography with Variant Hemoglobin A_{1c} Program (Bio-Rad Laboratories, Hercules, Calfornia, United States) (reference range 4.1%–6.5%). Fasting plasma glucose, alanine transaminase, plasma total cholesterol, high-density and low-density lipoprotein cholesterol, and triglycerides were measured with standard methods.

Plasma high-sensitivity CRP was measured by a particle-enhanced immunoturbimetric assay (Olympus Diagnostica GmbH, Hamburg, Germany) using anti-CRP gout monoclonal antibodies coupled to latex microparticles with a lower limit of detection (0.03 mg/l). The WBC count was performed using the ABBOTT CELL-DYN 1700 System automatic hematology analyzer (Diamond Diagnostics, Massachusetts, United States) and the ESR using the Westergren method.

Statistical methods For material description, standard statistic methods were used: frequencies for the categorical data mean and standard deviation for the normally distributed variables and quartiles for nonnormally distributed ones. The parametric T-test and nonparametric Mann-Whitney U test were applied for the continuous data comparison of normally or nonnormally distributed variables, respectively.

The CRP level was analyzed as a primary variable, and WBC and ESR were examined as secondary variables. In the comparison of mean values, differences with 95% confidence interval (CI) were calculated.

A *P*-value <0.05 was considered significant.

RESULTS

The clinical and laboratory characteristics for all groups are shown in TABLES 1 and 2.

Although there was no significant difference in age between the study groups, patients with type 2 diabetes had significantly higher BMI (32.4 kg/m^2) compared with diabetic and nondiabetic patients with HCV infection (28.5, 24.0, 26.4 kg/m^2, respectively). In addition, the duration of diabetes varied significantly between the diabetic groups (the longest was in patients with type 1 diabetes – 12.5 years).

TABLE 2 Histological findings of diabetic and nondiabetic patients with hepatitis C virus infection

	DM-HCV	Non-DM-HCV
mild fibrosis (F1), n	4	11
moderate fibrosis (F2), n	5	6
severe fibrosis (F3), n	9	1
cirrhosis (F4), n	1	–
no histological activity (G0), n	–	–
minimal activity (G1), n	6	4
mild activity (G2), n	11	16
moderate activity (G3), n	3	1
severe activity (G4), n	–	–

Abbreviations: see TABLE 1

The outcomes for primary and secondary endpoints are shown in TABLE 3. Serum CRP levels were lower in diabetic patients with HCV infection than in patients with type 2 diabetes (P <0.001) and higher than in HCV subjects (P = 0.002). The median values of CRP were 1.07, 2.58, 0.91, and 0.45 mg/l, respectively. There was no significant difference between the patients with diabetes and HCV and patients with type 1 diabetes (P = 0.747).

WBC count was significantly lower in diabetic HCV subjects than in type 2 diabetic patients (P = 0.029). The mean difference was with 95% CI: –0.87 (–1.64; –0.10). There were no differences between the other control groups.

For ESR, we found a significant difference only between diabetic patients with HCV and nondiabetic patients with HCV (P = 0.025); the corresponding medians were 10 and 5 mm/h.

DISCUSSION

Our study showed that high-sensitive CRP and WBC count are considerably lower in diabetic HCV patients compared with type 2 diabetic patients.

There is firm evidence to suggest that inflammatory markers are elevated in diabetic patients.[14] Nevertheless, the finding of lower CRP levels diabetic patients with HCV infection compared with diabetic patients without the infection may be surprising. This marker is produced in the liver under the influence of tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), the main inflammatory cytokines. Several authors reported the elevated levels of IL-6 and TNF-α in HCV patients.[15] Moreover, the majority of the established risk factors for diabetes in these patients, such as aging, black ethnicity, and a family history of diabetes, have been associated with increased TNF-α levels.[16]

TABLE 3 Serum concentration of inflammatory markers in study groups

Parameter	Patient groups			
	DM-HCV	T2DM	T1DM	Non-DM-HCV
CRP, mg/l				
median (quartile 25%; 75%)	1.07 (0.36; 2.45)	2.58 (1.22; 4.56) $P < 0.001$[a]	0.91 (0.42; 1.96) $P = 0.747$[a]	0.45 (0.22; 0.90) $P = 0.002$[a]
WBC count, G/l				
mean (SD)	6.65 (2.20)	7.52 (1.77) $P = 0.029$[b]	5.95 (1.57) $P = 0.064$[b]	6.26 (1.19) $P = 0.279$[b]
mean difference (95% CI)		–0.87 (from –1.64 to –0.10)	0.70 (from –0.03 to 1.43)	0.27 (from –0.31 to 1.07)
ESR, mm/h				
median (quartile 25%; 75%)	10 (3.5; 22)	8 (4.0; 12) $P = 0.532$	5 (3.0; 11) $P = 0.060$[a]	5 (2.5; 8.0) $P = 0.025$[a]

a Mann-Withney test; *P*-value is for comparison with the DM-HCV group, **b** T-test

Abbreviations: CI – confidence interval, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, WBC – white blood cell, others – see **TABLE 1**

Of note, type 2 diabetic patients demonstrated significantly higher values of BMI compared with diabetic HCV patients. There is a clear relationship between the amount of body fat and CRP levels in diabetic patients and patients with metabolic syndrome.[17,18] Therefore, the higher values of CRP observed in type 2 diabetic patients compared with diabetic patients with HCV infection may result from the higher rate of obesity. What is more, diabetic manifestation in patients with diabetes and HCV infection has been observed to be weaker (lower cholesterol levels and BMI).[19] Although diabetes in HCV patients is classified as type 2, these patients show the features of both type 1 and type 2 diabetes.[20] Moreover, the effect of chronic HCV infection makes this diabetic manifestation untypical.[21]

The behavior of acute-phase proteins (APPs) in HCV hepatitis has not been clarified. Shaheen et al.[22] found that the only inflammatory marker significantly linked with hepatitis C infection in patients with metabolic syndrome was ferritin. Yet it appears that diabetes, but not HCV infection, is an independent key factor causing ferritin elevation.[23] On the other hand, Lecube et al.[24] reported that proinflammatory cytokines such as TNF-α, its receptors, and IL-6 are increased in nondiabetic patients with HCV infection. In another study, CRP levels were higher in diabetic patients both with and without HCV infection in comparison with healthy controls, but no other significant differences were reported.[25] Finally, Kalabay et al.[26] observed significantly lower CRP levels in nondiabetic HCV patients.[26] Of interest, the levels of 2 negative APPs produced in the liver were markedly higher in HCV patients compared with healthy subjects. It may indicate that in chronic hepatitis C, the levels of APPs change in a direction that is opposite to that observed in the acute-phase response. This finding was also confirmed by Japanese authors who did not find any correlation between CRP levels and the liver histology or liver enzymes in contrast with HBV infection.[27]

On the other hand, CRP levels in diabetic HCV patients was still significantly higher than in nondiabetic HCV patients. Hyperglycemia may in part explain the observed difference between the groups. Moreover, CRP may be produced by extrahepatic mechanisms. Alternatively, hepatitis C may be linked with lower CRP levels. As a result, impaired liver function associated with chronic hepatitis C may lead to depressed production of CRP. Floris-Moore et al.[28] reported that among HIV-infected men, HCV infection was associated with decreased CRP levels.[28] However, Kalabay et al.[26] did not find any change in CRP among HCV patients who responded to interferon therapy. Thus, it suggests that other factors, apart from viral replication, may contribute to HCV-associated reduction in CRP levels. On the other hand, diabetic HCV patients were found to have more advanced fibrosis compared with nondiabetic ones. Despite the limited number of liver biopsies in our study, it still may suggest that progressive fibrosis may affect CRP levels.

In our study, WBC count was significantly higher in type 2 diabetic patients compared with diabetic HCV patients. Nevertheless, one might argue that the study patients were recruited from among those admitted to the hospital. Therefore, they might have had poor metabolic control and, consequently, more upregulated chronic inflammation. However, there was not a significant difference in HbA_{1c} between diabetic HCV patients and those with type 2 diabetes. Apparently, WBC is associated with metabolic syndrome and correlates with a number of its components.[29] On the other hand, WBC count is increased by cytokines, especially IL-6, which in fact is elevated in patients with HCV infection.

The lack of any difference in contrast with CRP and WBC may suggest that ESR is a less specific and less independent inflammatory marker. Never-

theless, diabetic patients have higher ESR compared with nondiabetic ones.

CRP and WBC count have been recognized as predictors of cardiovascular events. However, Danesh et al.[30] found that the strength of CRP as such a predictor is relatively moderate and it adds little to the value of traditional risk factors. Furthermore, it has been demonstrated that genetic variants associated with lifelong increase in CRP are not closely related with increased risk of cardiovascular disease.[31] Finally, in a large population-based study, no association between atherosclerotic endpoints and hepatitis C virus infection was found.[32]

In summary, diabetic patients with HCV infection seem to have decreased inflammatory markers compared with diabetic subjects without the infection. Hypothetically, this finding could be attributed to various HCV immunoinhibitory effects, for example via induction of interleukin-10, one of the cytokines associated with Th2 response favoring chronic infection.[33,34] Although our findings are definitely preliminary, it might be reasonable to adjust for the presence of HCV infection in the assessment of diabetic patients.

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