High Prevalence of Glucose Abnormalities in Patients With Hepatitis C Virus Infection

A multivariate analysis considering the liver injury

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OBJECTIVE — The aim of this study was to compare the prevalence of both impaired fasting glucose (IFG) and diabetes between hepatitis C virus (HCV)-infected patients and patients with other liver diseases but anti-HCV$^-$, taking into account the degree of liver damage.

RESEARCH DESIGN AND METHODS — A total of 642 consecutive patients attending the outpatient liver unit of a university hospital (498 anti-HCV$^+$ and 144 anti-HCV$^-$) were prospectively recruited. Patients were classified as having chronic hepatitis (n = 472) or cirrhosis (n = 170) by means of the result of either a liver biopsy or by typical clinical features. A logistic regression model was used to determine independent associations of covariates (age, sex, BMI, HCV antibody status, and triglycerides) with the presence of glucose abnormalities.

RESULTS — A threefold increase in the prevalence of glucose abnormalities was observed in HCV$^+$ patients with chronic hepatitis in comparison with HCV$^-$ subjects (32 vs. 12%; P = 0.0003). In contrast, among patients with cirrhosis, although both diabetes and IFG were more prevalent in anti-HCV$^+$ patients (40%) than in anti-HCV$^-$ patients (36%), the differences were not statistically significant. Finally, the logistic regression analysis showed that HCV infection was independently related to glucose abnormalities in those patients with chronic hepatitis (odds ratio 4.26 [95% CI 2.03–8.93]). In contrast, HCV was not an independent predictor of glucose abnormalities in cirrhotic patients.

CONCLUSIONS — The high prevalence of IFG and diabetes found in HCV-infected patients observed in our study suggests that screening for glucose abnormalities should be indicated in these patients. In addition, we provide evidence that the genuine connection between HCV infection and diabetes is initiated at early stages of hepatic disease.

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There is growing evidence to suggest an association between hepatitis C virus (HCV) infection and diabetes, two common disorders that cause devastating long-term complications in a significant number of patients. Several reports have found a high prevalence of HCV infection among diabetic patients (1–3). Additionally, a high prevalence of diabetes has also been reported in HCV-infected patients in comparison with other liver diseases (4–8). Recently, the Third National Health and Nutrition Examination Survey (NHANES III) has shown that people >40 years of age with HCV infection were more than three times more likely than those without HCV infection to have type 2 diabetes (9). However, some authors (10,11) have not observed an association between HCV infection and diabetes.

To further explore the link between HCV infection and diabetes, we have compared the prevalence not only of diabetes but also the impaired fasting glucose (IFG) (an early predictor of diabetes) between HCV-infected patients and patients with other HCV$^-$ liver diseases. The large cohort of HCV-infected patients included in the study has allowed us to evaluate separately patients with chronic hepatitis and patients with cirrhosis. This is an important confounding factor that should be considered in the analyses of the results, because glucose abnormalities are more frequent in patients with advanced liver disease. In addition, because some reports have suggested a relationship between specific HCV genotypes and some of the extrahepatic manifestations of HCV infection (12), we investigated the potential relationship of the different HCV genotypes on glucose abnormalities.

RESEARCH DESIGN AND METHODS

— From June 2000 to December 2001, a total of 642 consecutive patients of Caucasian origin attending the outpatient liver unit of a university hospital were recruited on a weekly basis. Anti-HCV$^+$ patients were referred from two main sources: from the blood bank of our hospital and from general practitioners. Patients were then divided into two groups according to their HCV antibody status: anti-HCV$^+$ (n = 498) and anti-HCV$^-$ (n = 144) patients. Exclusion criteria were previous treatment with either corticosteroids or interferon, a history of diabetic ketoacidosis, or age <30 years with insulin requirement (type 1 diabe-

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1 —*Clinical features of the 642 patients classified for anti-HCV status*

	Anti-HCV$^+$	Anti-HCV$^-$	*P*
n	498	144	
Age (years)	52.9 ± 14.1	54.7 ± 15.2	NS
Women/men (%)	45/55	51/49	NS
BMI (kg/m^2)	25.8 ± 4.2	26.2 ± 5.3	NS
Chronic hepatitis	380 (76.3)	92 (63)	NS
Cirrhosis	118 (23.7)	52 (36.1)	NS
Primary etiology			
HCV infection	498	—	
Alcoholic disease	—	46	
Hepatitis B virus infection	—	33	
Liver steatosis/steatohepatitis	—	29	
Autoimmune chronic hepatitis	—	15	
Primary biliary cirrhosis	—	14	
Cryptogenic	—	7	

Data are means ± SD or *n* (%).

tes), chronic pancreatitis, alcohol consumption >50 g per day, pancreatic tumor, combined hepatic disease (liver disease with more than one etiology), and concomitant infections (other infection apart from HCV infection).

Patients with cirrhosis were diagnosed by liver biopsy (compensated patients) or by typical clinical features such as signs of portal hypertension (splenomegaly, ascites, esofageal varices), hematological evidence of hypersplenism, or biochemical evidence of hepatocellular failure. Chronic hepatitis was diagnosed by liver biopsy in all patients in whom transaminases were elevated ($n = 285$) and in 91 of 187 patients with normal transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] less than upper limit of normality for three times during 6 months) (13). We defined normal transaminases as values within the 95th percentile of healthy subjects (AST, 12–40 UI/l and ALT, 8–44 UI/l for men; AST, 10–30 UI/l and ALT, 7–34 UI/l for women). For the anti-HCV$^+$ patients with normal transaminases and no liver biopsy ($n = 96$), we ensured that transaminases, liver function tests, and hepatic sonography were persistently normal.

Diabetes was defined on the basis of a history of therapy with oral hypoglycemic agents or insulin at the time of inclusion. In all patients not previously diagnosed, the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes (14) were used. Thus, diabetes was diagnosed if the fasting blood glucose was ≥7 mmol/l (126 mg/dl) on two separate occasions and IFG if the fasting blood glucose was between 6.1 mmol/l (110 mg/dl) and 7 mmol/l (126 mg/dl). In addition, a standard 2-h 75-g oral glucose tolerance test (OGTT) was performed on the first 50 anti-HCV$^+$ nondiabetic patients with chronic hepatitis included in the study. Fifty anti-HCV$^-$ patients equipared by age, BMI, and sex were selected among nondiabetic control subjects with chronic hepatitis who agreed to have an OGTT performed. In this group, diabetes and impaired glucose tolerance (IGT) were diagnosed according to a 2-h plasma glucose concentration of ≥11.1 mmol/l (200 mg/dl) and 7.8–11.09 mmol/l (140–200 mg/dl), respectively. Based on the clinical information, all diabetic patients in this study were assumed to have type 2 diabetes. Informed written consent was obtained from all participants, and the study was approved by the hospital's human ethics committee.

Laboratory analysis

Serological testing for anti-HCV was done using a second-generation commercial enzyme immunoassay (Abbot Laboratories, Chicago, IL) according to the manufacturer's instructions. All serum samples that were found to be anti-HCV reactive were also analyzed using an immunoblot assay (LIA-HCV-3; Sorin Biomedica, Saluggia, Italy) to confirm HCV specificity. In addition, all anti-HCV$^+$ patients with normal transaminases were HCV RNA$^+$ confirmed either during HCV genotyping or by HCV RNA qualitative testing (Amplicor; Roche Molecular Systems, Branchburg, NJ).

The HCV genotype was determined in 247 of the 498 (49.6%) anti-HCV$^+$ patients. HCV genotyping was performed by RT-PCR on a segment from the core region and by hybridization of this fragment with oligonucleotide-specific probes according to the manufacturer's instruction (HCV Genotyping, DNA Enzyme Immunoassay; DiaSorin, Saluggia, Italy). The assay is designed to recognize the 1a, 1b, 2a, 2b, 3, 4, 5, and 6 HCV genotypes. All patients with mixed HCV genotypes were excluded.

Statistical analysis

Comparisons between groups (anti-HCV$^+$ and anti-HCV$^-$) were done using the Student's *t* test for continuous variables and the χ^2 test for categorical data. Results are expressed as the mean ± SD. A multivariate logistic regression analysis considering age, sex, HCV antibody status, BMI, and triglycerides as independent variables and glucose abnormalities (IFG and diabetes) as the dependent variable was separately performed on the whole group of patients, patients with chronic hepatitis, and patients with cirrhosis. All *P* values are based on a two-sided test of statistical significance. Significance was accepted at the level of $P < 0.05$.

RESULTS — The main clinical characteristics of patients included in the study and the prevalence of glucose abnormali-

Table 2 —*Prevalence of glucose abnormalities in anti-HCV$^+$ and anti-HCV$^-$ patients according to their degree of liver disease*

	Anti-HCV$^+$	Anti-HCV$^-$	*P*
All patients			
n	498	144	
Diabetes	23	18	NS
IFG	14	6	0.007
IFG + diabetes	37	24	0.005
Chronic hepatitis			
n	380	92	
Diabetes	17	7	0.03
IFG	15	5	0.009
IFG + diabetes	32	12	0.0003
Cirrhosis			
n	118	52	
Diabetes	40	36	NS
IFG	12	7	NS
IFG + diabetes	52	43	NS

Data are percent.

Table 3 —*Logistic regression analysis considering age, sex, HCV antibody status, degree of liver disease, BMI, and triglycerides as independent variables and glucose abnormalities (IFG and diabetes) as the dependent variable*

	P	Odds ratio (95% CI)
All patients (n = 642)		
Anti-HCV status (negative/positive)	0.001	2.26 (1.47–3.70)
Degree of liver disease (chronic hepatitis/cirrhosis)	0.005	1.86 (1.21–2.86)
Sex (men/women)	0.022	1.56 (1.07–2.29)
BMI (kg/m^2)	0.002	1.11 (1.04–1.19)
Age (years)	0.000	1.06 (1.05–1.07)
Triglycerides (>1.7 mmol/l)	NS	—
Chronic hepatitis (n = 472)		
Anti-HCV status (negative/positive)	0.000	4.26 (2.03–8.93)
Sex (men/women)	0.002	2.16 (1.33–3.49)
BMI (kg/m^2)	0.005	1.12 (1.04–1.22)
Age (years)	0.000	1.07 (1.04–1.08)
Triglycerides (>1.7 mmol/l)	NS	—
Cirrhosis (n = 170)		
Anti-HCV status (negative/positive)	NS	—
Sex (men/women)	NS	—
BMI (kg/m^2)	0.047	1.15 (1–1.33)
Age (years)	0.002	1.05 (1.02–1.08)
Triglycerides (>1.7 mmol/l)	NS	

The analysis was done for the whole of patients, patients with chronic hepatitis, and patients with cirrhosis. Overall predictive value for the model: 76% (all patients), 75% (chronic hepatitis), and 80% (cirrhosis).

ties are shown in Tables 1 and 2, respectively. We have not detected any difference in the main confounding factors (age, BMI, and stage of liver disease) between anti-HCV$^+$ and anti-HCV$^-$. Diabetes was more prevalent among patients with HCV infection (23%) than among anti-HCV$^-$ patients (18%), but this difference was not statistically significant. However, the prevalence of IFG was significantly higher in patients with HCV infection compared with anti-HCV$^-$ patients (14 vs. 6%; P = 0.007). When both categories of abnormalities of glucose metabolism were considered (diabetes and IFG), the differences between both groups remained at a significant level (37 vs. 24%, P = 0.005).

In the group of patients with chronic hepatitis, both diabetes and IFG were significantly more prevalent among anti-HCV$^+$ patients than in those anti-HCV$^-$ (Table 2). In addition, when patients with normal transaminases (n = 187) were examined, the differences remained statistically significant (24% [anti-HCV$^+$] vs. 5% [anti-HCV$^-$]; P = 0.003). In contrast, among patients with cirrhosis, although both diabetes and IFG were more prevalent in anti-HCV$^+$ patients than in anti-HCV$^-$ patients, the differences were not statistically significant (Table 2).

The logistic regression analysis showed that HCV infection was independently related to glucose abnormalities (Table 3). The odds ratio for HCV infection was 2.26 (95% CI 1.47–3.70) when all patients were included and 4.26 (2.03–8.93) in patients with chronic hepatitis. In contrast, HCV was not an independent predictor of glucose abnormalities in cirrhotic patients.

The results of OGTT performed in the subset of patients with chronic hepatitis in whom diabetes was not diagnosed using the fasting plasma glucose according the American Diabetes Association criteria are shown in Table 4. OGTT enabled us to diagnose nine (18%) new cases of diabetes and 15 (30%) of IGT in anti-HCV$^+$ patients, these figures being significantly higher than those obtained in anti-HCV$^-$ patients (P = 0.02 and P = 0.04, respectively).

The HCV genotype distribution observed in our study was: 207 patients with genotype 1 (83.8%), 12 patients with genotype 2 (4.8%), 18 patients with genotype 3 (7.3%), and 10 patients with genotype 4 (4%). Differences in the prevalence of glucose abnormalities among these four genotypes were not observed (genotype 1, 39.1%; genotype 2, 33%; genotype 3, 16%; genotype 4, 33%; NS). In addition, when only patients with chronic hepatitis were considered, the prevalence was very similar in all groups (20% for genotype 1; 14.3% for genotype 2; 20% for genotype 3; 22.2% for genotype 4).

CONCLUSIONS — To our knowledge, this is the first study in which the prevalence of both IFG and diabetes has been evaluated in a large cohort of HCV-infected patients, taking into account the degree of liver damage. In HCV$^+$ patients with chronic hepatitis, we observed a threefold increase in the prevalence of glucose abnormalities in comparison with HCV$^-$ subjects (32 vs. 12%). However, in patients with cirrhosis, although a high frequency of glucose abnormalities were detected, differences in the prevalence of either diabetes or IFG between anti-HCV$^+$ and anti-HCV$^-$ patients were not found. These findings suggest that the genuine connection between HCV infection and diabetes is initiated at early stages of hepatic disease. In this regard, it should be emphasized that in HCV-infected patients with chronic hepatitis and normal transaminases, we have detected a fivefold higher prevalence of diabetes than that found among anti-HCV$^-$ patients.

Fourteen years after the discovery of the HCV, this infection has been recognized as a major cause of chronic liver disease worldwide, affecting ~3% of the world population (15). Recent studies indicate that the rate of progression to advanced liver disease may be lower than previously assumed. Alter and Seeff (16) have proposed that only a minority of in-

Table 4 —*Main clinical features and prevalence of diabetes and IGT using 2-h glucose criteria in patients with chronic hepatitis in whom diabetes was not diagnosed by fasting glucose criteria*

	Anti-HCV$^+$	Anti-HCV$^-$	*P*
n	50	50	
Age (years)	56 ± 11	54 ± 14	NS
Men/women (%)	22/28	19/31	NS
BMI (kg/m^2)	25.5 ± 4.9	27.6 ± 5.1	NS
Diabetes	9 (18)	2 (4)	0.02
IGT	15 (30)	9 (18)	0.04

Data are means ± SD or n (%). Diabetes and IGT were diagnosed according to 2-h plasma glucose concentration of ≥11.1 mmol/l (200 mg/dl) and 7.8–11.09 mmol/l (140–200 mg/dl), respectively.

fections lead to severe, progressive liver disease. In a recent epidemiological study, Salomon et al. (17) estimated the median duration between infection and cirrhosis to be 46 years for men infected at age 25 years, whereas in a cohort of women infected at this age, fewer than 30% will progress to cirrhosis even after 50 years of infection. As public health campaigns encourage individuals with potential risk factors to be tested for HCV, the possibility that progression rates are lower than previously estimated will be an important consideration when making decisions about treatment recommendations and health policy toward patients with chronic HCV infection. In this regard, the high prevalence of both IFG and diabetes found in HCV-infected patients observed in our study suggests not only that screening for diabetes should be indicated in these patients but also that all of the measures to achieve its therapeutic goals should be implemented. Furthermore, the high percentage of new cases of diabetes that we have detected using postload hyperglycemia in the subset of patients with chronic hepatitis suggests that OGTT should be recommended as the primary screening test for diabetes in these patients.

If HCV infection is the cause of diabetes or, by contrast, diabetic patients are more prone to acquire HCV infection has been a subject of debate. We previously reported the absence of any particular epidemiological factor for HCV infection among the diabetic population (2). Recently, in the NHANES III, the age-adjusted odds ratio of type 2 diabetes in individuals with both HCV RNA and HCV antibody was 2.48 (95% CI 1.23–5.01) compared with 0.98 for subjects with HCV antibody but not RNA (18). In addition, in the present study, we have shown that not only diabetes but also IFG are more prevalent in HCV-infected patients. Taken together, these findings are not consistent with the assumption that diabetes leads to HCV infection and support the hypothesis that persistent HCV infection is associated with the subsequent development of diabetes. The specific mechanisms responsible for the development of diabetes in HCV-infected patients are not fully understood, but it seems that an increase of insulin resistance associated with either body iron stores, hepatic steatosis, or tumor necrosis factor-α could play an important role (19–23). By contrast, the autoimmune basis of diabetes associated to HCV infection has been previously ruled out (24).

There are only a few reports evaluating the relationship between HCV genotypes and diabetes (3,8,11). In the present study, a much larger number of patients than previously has been included, and no differences in the prevalence of either IFG or diabetes among HCV genotypes were observed. The lower prevalence of glucose abnormalities observed in patients with genotype 3 could be attributed to the lower prevalence of cirrhosis due to the younger age of this group (data not shown). However, because there are four main HCV genotypes with a very different prevalence, the sample size used in the present study is still not large enough for a definitive conclusion to be obtained.

In summary, HCV-infected patients present a high prevalence of both IFG and diabetes in comparison with non–HCV-infected patients with other liver diseases. This finding is mainly due to the group of patients with chronic hepatitis. Because HCV infection is an important predictor of diabetes, testing for glucose abnormalities should be mandatory for these patients. Further studies to clarify the mechanisms involved in this association are needed to design specific strategies to prevent diabetes in HCV-infected patients.

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