Sustained Virological Response Correlates With Reduction in the Incidence of Glucose Abnormalities in Patients With Chronic Hepatitis C Virus Infection

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OBJECTIVE — There is evidence to suggest that hepatitis C virus (HCV) infection is a high-risk condition for developing type 2 diabetes. However, there are no interventional studies that confirm that HCV infection causes diabetes. The main aim of this study was to compare the incidence of glucose abnormalities (diabetes plus impaired fasting glucose) between HCV-infected patients with or without sustained virological response (SVR) after antiviral therapy.

RESEARCH DESIGN AND METHODS — Patients with normal fasting glucose (<100 mg/dl) with biopsy-proven chronic hepatitis C without cirrhosis and with at least 3 years of follow-up after finishing antiviral therapy were included in the study ($n = 234$). Patients received interferon α-2b (alone or with ribavirin) for 6 or 12 months according to genotype. Cumulative incidence of glucose abnormalities was evaluated by using the Kaplan-Meier method comparing subjects with and without a SVR to antiviral treatment. A multivariate Cox proportional hazards analysis was performed to explore the variables independently associated with the development of glucose abnormalities.

RESULTS — During follow-up, 14 of 96 (14.6%) patients with SVR and 47 of 138 (34.1%) nonsustained responders developed glucose abnormalities ($P = 0.001$). Patients with SVR did not develop diabetes during follow-up, whereas nine cases of diabetes were detected in nonsustained responders ($P = 0.007$). After adjustment for the recognized predictors of type 2 diabetes, the hazard ratio for glucose abnormalities in patients with SVR was 0.48 (95% CI [0.24–0.98], $P = 0.04$).

CONCLUSIONS — Our results provide evidence that eradication of HCV infection significantly reduces the incidence of glucose abnormalities in chronic hepatitis C patients. In addition, this study supports the concept that HCV infection causes type 2 diabetes.

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Large community-based studies have found a strong association between hepatitis C virus (HCV) infection and type 2 diabetes (1,2), two common disorders that cause devastating long-term complications in a significant number of patients. In addition, a high prevalence of both diabetes and impaired fasting glucose (IFG), an early predictor of diabetes, has been reported in patients with chronic hepatitis C compared with other chronic liver diseases (3–7). Furthermore, in HCV-infected patients with chronic hepatitis and normal transaminases, we have detected a fivefold higher prevalence of diabetes than that found in anti-HCV–negative patients (24 vs. 5%, $P = 0.003$) (7). Therefore, it seems that the genuine connection between HCV infection and diabetes is initiated at the early stages of hepatic disease.

HCV infection is characterized by a silent onset in most infected individuals, and recent studies (8–10) indicate that the rate of progression to advanced liver disease is lower than previously assumed. Salomon et al. (10) 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% would progress to cirrhosis even after 50 years of infection. This low progression rate is an important consideration when making decisions about treatment recommendations and health policy toward patients with chronic HCV infection. Moreover, the large reservoir of chronically HCV-infected individuals under the age of 50 who became infected in the early 1980s (when the incidence rates were highest) will reach the age at which diabetes typically occurs during the next decade. This raises the intriguing question of whether the rise in HCV infection is contributing to the increasing prevalence of type 2 diabetes.

The specific mechanisms by which HCV leads to type 2 diabetes are not fully understood, but an increase of insulin resistance associated with both steatosis and overproduction of proinflammatory cytokines could play a crucial role (11–13). In vitro experiments with liver samples indicate that HCV infection leads to a postreceptor defect in insulin receptor substrate 1, thereby contributing to insulin resistance (14). Furthermore, Shintani et al. (15) have recently shown direct experimental evidence for the contribution of HCV in the development of insulin resistance using HCV core transgenic mice.

Although there is growing evidence to support the concept that HCV infection is a risk factor for developing type 2 diabetes, there have been no interventional studies confirming this issue. The aim of this study was to analyze for the first time

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Abbreviations: AST, aspartate aminotransferase; GT, glutamyltranspeptidase; HCV, hepatitis C virus; IFG, impaired fasting glucose; SVR, sustained virological response.

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

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Table 1—*Comparison of baseline characteristics of the study cohort according SVR*

	SVR	No SVR	*P*
n	96	138	
Age (years)	41.6 ± 9.7	43.6 ± 10.6	0.13
Sex (male/female)	59.3/40.7	63.3/36.7	0.31
BMI (kg/m^2)	24.7 ± 4.4	25.0 ± 3.3	0.75
BMI >30 kg/m^2	6.2	5.8	0.66
Triglycerides (mg/dl)	85 ± 27	91 ± 67	0.11
Triglycerides >150 mg/dl	4.1	8.6	0.27
Blood pressure ≥130/80 mmHg	7.3	6.5	0.97
AST (units/l)	49 ± 32	63 ± 55	0.03
ALT (units/l)	84 ± 68	101 ± 99	0.15
γ-GT (units/l)	37 ± 45	52 ± 39	0.01
Fibrosis	2.26 ± 0.9	2.38 ± 1.08	0.43
Genotype 1	70	88	<0.001
Treatment duration (months)	10.7 ± 2.9	10.8 ± 3.3	0.51

Data are means ± SD or percent. Comparisons between groups were made using the Student's *t* test for continuous variables and the χ^2 test for categorical variables. ALT, alanine aminotransferase.

whether HCV clearance results in a reduction in the incidence of glucose abnormalities (IFG and diabetes) and, therefore, to confirm HCV as a new diabetogenic agent.

RESEARCH DESIGN AND METHODS

— A total of 610 patients with chronic hepatitis C who received antiviral treatment (interferon alone or with ribavirin), between 1993 and 2001, as outpatients of the Liver Unit of our hospital were evaluated for the study. Entry criteria included anti-HCV– and HCV RNA–positive patients aged >18 years with a liver biopsy before treatment and at least 3 years of follow-up after finishing antiviral therapy. Exclusion criteria were *1*) fasting plasma glucose level ≥100 mg/dl (≥5.6 mmol/l) or prior diagnosis of either diabetes or IFG, *2*) active alcohol consumption (>40 g/day for men and >20g/day for women [16]) or features of alcoholic disease in the liver biopsy, *3*) presence of severe liver fibrosis with nodules in the liver biopsy, which is fibrosis stages 5–6 based on Ishak's classification (17) (the reason for the exclusion of these patients was to avoid the glucose abnormalities associated with advanced liver disease rather than HCV infection), *4*) duration of antiviral therapy <6 months, and *5*) presence of other concomitant diseases or conditions such as HIV infection, hepatitis B, autoimmune hepatitis, hemochromatosis, primary biliary cirrhosis, Wilson's disease, α_1-antitrypsin deficiency, and neoplasia.

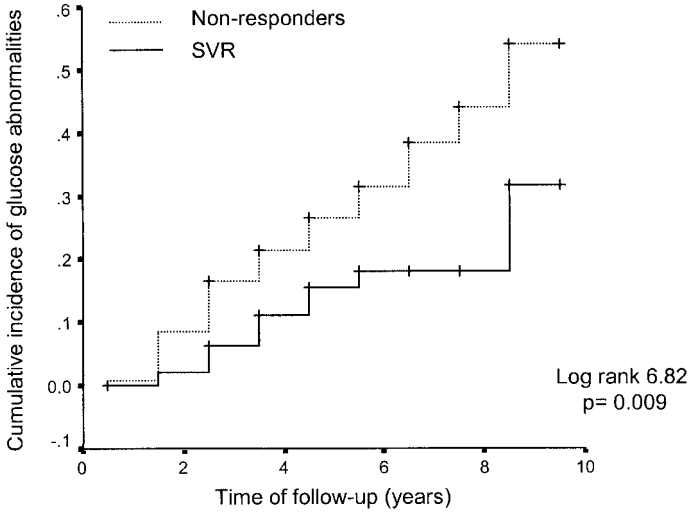

Figure 1—*Kaplan-Meier estimates of the cumulative incidence of glucose abnormalities during follow-up among patients with SVR* (n = *96) and nonsustained responders* (n = *138).*

Overall, 376 patients were excluded from further assessment, leaving 234 patients for the study. All these patients have been followed-up every 6 months by means of clinical examination and laboratory testing as outpatients of the Liver Unit. HCV genotyping was as follows: genotype 1 (79.1%), genotype 2 (3.5%), genotype 3 (11.9%), and genotype 4 (5.5%). Eighty (34%) patients received interferon α-2b alone (Intron-A; Schering-Plough, Kenilworth, NJ) at a dose of 3 million units three times per week, while 154 (66%) patients were treated with interferon α-2b plus ribavirin (Rebetron; Schering-Plough) at a dose of 800–1,200 mg/day. Duration of therapy was carried out according to genotype: 6 months for genotypes 2 and 3; 12 months for genotypes 1 and 4. Sustained virological response (SVR) was defined by an HCV RNA negative in one single sample after 6 months of completing therapy. Another sample was obtained 6 months later (12 months after the conclusion of treatment) in order to confirm HCV RNA negativity. No patient HCV RNA negative after 6 months of finishing treatment (SVR) became HCV RNA positive in the analysis performed 12 months after completing antiviral therapy. The follow-up started 6 months after completion of treatment (when the measurement for the definition of SVR was made). The mean duration of follow-up was 5.7 ± 2.1 years (range 2.5–9.5), and it was similar for patients with SVR and nonsustained responders. A liver biopsy was available before therapy in all included patients. Fibrosis staging was performed according to Ishak's classification (17).

According to the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, diabetes was defined as fasting plasma glucose ≥126 mg/dl (7 mmol/l) in two separate measurements and IFG was defined as baseline glucose levels 100–125 mg/dl (5.6–6.9 mmol/l) (18). Based on the clinical information, all new cases of diabetes during follow-up were type 2 diabetes. The study was consistent with the principles of the Declaration of Helsinki, and it was approved by the hospital's human ethics committee.

Laboratory assessments

After overnight fasting, blood samples were drawn for routine analyses such as determination of glucose, alanine aminotransferase, aspartate aminotransferase (AST), γ glutamyltranspeptidase (GT), and triglycerides. These parameters were measured by standard laboratory tech-

Table 2—*Comparison of baseline characteristics of the study cohort between patients who develop glucose abnormalities after antiviral therapy and patients remaining normoglycemic*

	IFG + diabetic patients	Normoglycemic patients	*P*
n	61	173	
Age (years)	46.1 ± 10	41.6 ± 10	0.003
Sex (male/female)	54.1/45.9	64.2/35.8	0.21
BMI (kg/m^2)	26.1 ± 4.7	24.3 ± 3.1	0.02
AST (units/l)	67 ± 72	53 ± 34	0.15
ALT (units/l)	109 ± 117	89 ± 75	0.13
γ-GT (units/l)	65 ± 62	39 ± 29	<0.001
Triglycerides (mg/dl)	103 ± 41	85 ± 59	0.04
Fibrosis score	2.41 ± 0.72	2.23 ± 0.86	0.13
Genotype 1	75.4	71.1	0.28
SVR	23	47.4	0.006

Data are means ± SD or percent. Comparisons between groups were made using the Student's *t* test for continuous variables and the χ^2 test for categorical variables. ALT, alanine aminotransferase.

niques used in clinical chemistry laboratories. All patients had positive anti-HCV as measured by a second-generation commercial enzyme immunoassay (Abbott Laboratories, Chicago, IL) and positive HCV RNA in serum (Amplicor; Roche, Montclair, NJ). All patients were negative for hepatitis B surface antigen (Abbott Laboratories) and anti-HIV (Abbott Laboratories).

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.

Statistical analysis

Comparisons between SVR and non-SVR groups were made using the Student's *t* test for continuous variables and the χ^2 or Fisher's exact test for categorical variables. Survival curves (Kaplan-Meier method) were calculated to estimate the cumulative incidence of glucose abnormalities according to the response to antiviral therapy (SVR vs. no SVR). The difference between these two groups in the incidence of glucose abnormalities was tested by means of the two-sided log-rank test. To further define the importance of the response to antiviral treatment and other baseline variables, a Cox proportional hazards regression model (stepwise regression with backward selection of independent variables) was applied to the primary end point (glucose abnormalities). Apart from SVR, the following covariates (independent variables) with potential influence on diabetes development were included: age, BMI, AST, alanine aminotransferase, γ-GT, triglycerides, fibrosis score, genotype, and treatment duration. The patient follow-up for the Kaplan-Meier and Cox regression analysis started after the definition of SVR or non-SVR was made, i.e., 6 months after completing the antiviral treatment. All analyses were performed using SSPS software (version 10.0; SPSS, Chicago, IL).

RESULTS — A sustained virological response was obtained in 96 of the 234 (41%) patients treated (32% with interferon alone and in 68% with interferon plus ribavirin). The characteristics of the patients at the beginning of the study according to response to antiviral therapy are summarized in Table 1. γ-GT, AST, and HCV genotype were associated with SVR rate. By contrast, we did not observe any significant difference in age, BMI, triglycerides, and the degree of liver fibrosis. The percentage of patients with any component of the metabolic syndrome (BMI >30 kg/m^2, triglycerides >150 mg/dl, or blood pressure ≥130/85 mmHg) was similar in both groups.

During follow-up, 14 of the 96 (14.6%) patients with SVR and 47 of 138 (34.1%) nonsustained responders developed glucose abnormalities ($P = 0.001$). IFG was detected in 14 (14.6%) patients with SVR, whereas it was found in 38 (27.5%) nonsustained responders ($P = 0.02$). Patients with SVR did not develop diabetes during follow-up, whereas nine cases of diabetes were detected in nonsustained responders ($P = 0.007$). The cumulative incidence of glucose abnormalities in patients with SVR compared with nonsustained responders is shown in Fig. 1.

The baseline clinical features of the whole group of patients according to development, or not, of glucose abnormalities are summarized in Table 2. In univariate analysis, the variables associated with the development of diabetes were age, BMI, triglycerides, γ-GT, and SVR. The follow-up was similar in patients who developed glucose abnormalities and in patients who maintained normoglycemia (6.03 ± 2.4 vs. 5.7 ± 2.2 years; $P = 0.1$). In addition, we did not find any significant difference in treatment duration between patients who developed glucose abnormalities after antiviral therapy and those who maintained normoglycemia (11.1 ± 2.9 vs. 10.8 ± 3.3 months; $P = 0.53$).

The univariate hazard ratios (HRs) for the development of glucose abnormalities for the variables included in the study are displayed in Table 3. After adjustment for the recognized predictors of both type 2 diabetes and SVR, the HR for glucose ab-

Table 3—*Univariate HRs for the development of glucose abnormalities corresponding to the main variables included in the study*

	HR (95% CI)	*P*
Age (years)	1.029 (1.007–1.052)	0.01
Sex (male/female)	0.768 (0.35–1.68)	0.31
BMI (kg/m^2)	1.088 (1.006–1.176)	0.035
AST (per 50 units/l)	1.303 (1.061–1.601)	0.012
ALT (per 50 units/l)	1.138 (1.007–1.287)	0.039
γ-GT (per 50 units/l)	1.526 (1.221–1.908)	<0.0001
Triglycerides (per 50 mg/dl)	1.234 (1.040–1.464)	0.016
Fibrosis score	1.311 (1.013–1.698)	0.04
Genotype 1 (yes/no)	1.304 (0.585–2.903)	0.51
SVR (yes/no)	0.498 (0.278–0.890)	0.018

ALT, alanine aminotransferase.

Table 4—*Independent predictors of glucose abnormalities (IFG plus diabetes) using a multivariate Cox regression proportional hazards model*

Variable	Adjusted HR (95% CI)	*P*
SVR (yes/no)	0.48 (0.24–0.98)	0.04
Baseline triglycerides (per 50 mg/dl)	1.204 (1.020–1.422)	0.03
Baseline γ-GT (per 50 units/l)	1.565 (1.211–2.202)	0.001

Model was also adjusted for age (HR 1.015 [95% CI 0.731–1.386], $P = 0.35$), BMI (1.066 [0.963–1.179], $P = 0.21$), AST (per 50 units/l) (1.289 [0.572–2.907], $P = 0.54$), alanine aminotransferase (per 50 units/l) (0.98 [0.608–1.537], $P = 0.18$), fibrosis score (1.167 [0.827–1.643], $P = 0.37$), genotype (1.001 [0.371–2.696], $P = 0.99$), and duration of treatment (0.992 [0.384–2.539], $P = 0.87$).

normalities in patients with SVR was 0.48 ([95% CI 0.24–0.98], $P = 0.04$) compared with patients without SVR. Apart from SVR, baseline γ-GT and triglycerides were also independently associated with diabetes development (Table 4).

CONCLUSIONS — Although there is emerging evidence to suggest that HCV could lead to type 2 diabetes, there are no interventional studies confirming this issue. In the present study, we have shown that in chronic hepatitis C, the response to antiviral therapy is independently related to the development of glucose abnormalities after adjusting for the main recognized predictors for type 2 diabetes development. Therefore, patients with chronic hepatitis C with SVR after antiviral treatment are 0.48 times as likely to develop glucose abnormalities during follow-up as patients without SVR. These findings provide evidence that eradication of HCV infection dramatically reduces the incidence of both IFG and type 2 diabetes in chronic hepatitis C patients. The potential impact on health-related costs of the present results is quite significant if we consider that antiviral therapy for hepatitis C cannot only eradicate HCV infection but also prevent the development of diabetes.

It has been previously demonstrated that the incidence of diabetes among HCV-infected patients appears to be modified by recognized diabetes risk factors. Mehta et al. (19), in a prospective analysis performed in a large community-based cohort, observed that subjects with HCV infection were more likely to develop type 2 diabetes than patients without HCV infection, in particular when other recognized diabetes risk factors such as advanced age and higher BMI coexisted. Similarly, in our study, patients who developed glucose abnormalities had more diabetes risk factors such as older age, higher BMI, and triglycerides at baseline compared with patients who remained without glucose abnormalities. Therefore, apart from SVR, the diabetes risk factors above mentioned could be helpful in identifying those patients at risk of developing diabetes.

Insulin resistance seems to be related to poor response to antiviral treatment in chronic hepatitis C patients (20). Therefore, it could be argued that the higher incidence of glucose abnormalities detected in nonsustained responders might be attributed to classical factors associated with insulin resistance rather than to the persistence of HCV. However, it should be noted that in HCV-infected patients included in the present study, no significant differences were observed between SVR and non-SVR in the main general risk factors associated with diabetes development. In addition, the percentage of patients with components of metabolic syndrome was very low and there were no differences between SVR and non-SVR. Therefore, a potential bias due to the different therapeutic responses conditioned by insulin resistance is very unlikely. Finally, the response to antiviral therapy was independently related to the development of glucose abnormalities in a multivariate Cox proportional hazard regression model. Taken together, our findings suggest that the higher incidence of glucose abnormalities observed in the non-SVR group was mainly due to the persistence of HCV rather than other classical predictors of type 2 diabetes.

The specific mechanisms involved in the pathogenesis of diabetes associated with HCV remain to be elucidated. HCV infection has been linked to immunologic disorders such as cryoglobulinemia, glomerulonephritis, thyroiditis, and Sjöegren syndrome (21). In addition, HCV shares regional amino acid homology with GAD antibody (22). It might then be thought that HCV could trigger an immune reaction against the β-cell, which leads to diabetes. However, none of the studies that have examined the presence of islet cell antibodies in HCV-infected patients have found an increased frequency (23–27). In addition, we have recently demonstrated that an impairment in insulin secretion is not a primary mechanism accounting for diabetes associated with HCV infection (13). By contrast, it seems that insulin resistance mediated by proinflammatory cytokines plays an essential role (12,13). It has been recently demonstrated that the clearance of the virus in chronic hepatitis C patients induced an improvement in insulin resistance (20). Therefore, this could be the mechanism by which SVR prevents the development of diabetes. However, in the present study, a direct measure of insulin resistance was not performed and, therefore, we cannot confirm this issue. Future studies measuring insulin resistance, viral load, and proinflammatory cytokines before and after antiviral therapy would be useful to further understand the mechanisms by which the eradication of HCV infection could prevent diabetes development.

In the present study, apart from SVR, baseline triglycerides and γ-GT were also independently related to the incidence of glucose abnormalities. Regarding γ-GT, it should be noted that it has been closely associated with hepatic steatosis and insulin resistance (28–30) and proposed both as a simple and reliable marker of visceral and hepatic fat and also of hepatic insulin resistance. Furthermore, several prospective studies performed in large cohorts of British (31), Finnish (32), Japanese (33), and Korean (34) populations have demonstrated that serum γ-GT is an independent predictor for developing metabolic syndrome and diabetes. Therefore, it is not surprising that γ-GT was an independent risk factor for diabetes development in our cohort. Finally, serum levels of triglycerides, another surrogate of insulin resistance (35–37) and a well-known predictor of type 2 diabetes, were also independently related to the development of glucose abnormalities. In conclusion, our results provide evidence that clearance of HCV significantly reduces the development of glucose abnormalities in chronic hepatitis C subjects. Furthermore, this study supports the concept that HCV is a diabetogenic agent.

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