

Hepatitis C Virus Infection

Evidence for an association with type 2 diabetes

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An increased prevalence of type 2 diabetes and impaired glucose tolerance has been consistently found in liver cirrhosis from any cause (1–3). Less clear is whether hepatitis C virus (HCV) infection is associated with type 2 diabetes in the absence of cirrhosis. Several reports have claimed a specific association between HCV infection and type 2 diabetes, but in most instances, patients were a mixture of cases with cirrhosis and hepatitis (4–6). Two clinic-based studies found an excess of type 2 diabetes in non-cirrhotic HCV⁺ (NC-HCV⁺) patients compared with patients with chronic hepatitis of other origin (7–9), but another large study could not detect it (10). Furthermore, one clinic-based small study found a specific association with type 2 diabetes in NC-HCV⁺ patients (11) compared with a general population sample.

The aim of this study was to establish the prevalence and clinical phenotype of type 2 diabetes in a large series of NC-HCV⁺ patients. A sample of the general population or patients with hepatitis B virus (HBV)-related noncirrhotic chronic hepatitis (NC-HBV⁺) was used as control subjects.

RESEARCH DESIGN AND

METHODS— From January 1995 to December 2001, 564 NC-HCV⁺ patients were consecutively examined at our center (none had been previously treated with interferon). Diagnosis of HCV infec-

tion was based on abnormal serum aminotransferases levels of >6 months' duration and positive testing for serum anti-HCV markers and HCV-RNA, as previously reported (12). Liver biopsy was performed (following clinical indication) (10,12) in 403 patients. Patients with cirrhosis (by histology, laboratory evidence of liver failure, and/or ultrasound-proven portal hypertension) (10,12) or hepatocellular carcinoma were excluded. Among 550 subjects randomly extracted from the general registry of northwest Tuscany and systematically screened for thyroid disorders, 302 individuals >50 years of age were used as a population-based age-matched control group. Subjects with a history of alcohol abuse, drug addiction, or positivity for markers of viral hepatitis were excluded. Furthermore, 82 patients >40 years of age with NC-HBV⁺ (10) were consecutively screened. Diagnosis of NC-HBV⁺ was based on abnormal serum aminotransferases levels for >6 months and positive testing for HBV-DNA, as previously reported (13).

Type 2 diabetes was diagnosed as a fasting plasma glucose level ≥ 7.0 mmol/l on more than one occasion; subjects on treatment with oral hypoglycemic agents were also considered type 2 diabetic patients (10). Patients with type 1 diabetes were excluded (10). In all study subjects, fasting plasma glucose, cholesterol, triglycerides, international normalized ratio, and platelet counts were measured by conventional methods (12). Written in-

formed consent was obtained from all study subjects.

Data are given as means \pm SD. Group differences were analyzed by the χ^2 test or relative risk (RR) for categorical variables and two-way ANOVA for continuous variables (with diabetes and HCV positivity as the factors).

RESULTS— As shown in Table 1, NC-HCV⁺ patients, NC-HBV⁺ patients, and control subjects were well matched for sex and age. Mean international normalized ratio (1.09 [range 0.83–1.29]) and platelet counts (313,000/ μ l [134,000–436,000]) in the NC-HCV⁺ group were not significantly different from those in the NC-HBV⁺ (1.11 [0.81–1.32] and 306,000/ μ l [128,000–443,000], respectively) and control (1.06 [0.85–1.25] and 316,000/ μ l [131,000–452,000], respectively) groups.

The features specifically associated with HCV⁺ were a lower BMI and reduced serum total and LDL cholesterol concentrations. The prevalence of type 2 diabetes was significantly higher in NC-HCV⁺ patients (12.6%) compared with control subjects (7.0%) or NC-HBV⁺ patients (4.9%) ($\chi^2 = 9.6$, $P = 0.008$). The RR for type 2 diabetes in NC-HCV⁺ patients was 1.81 (95% CI 1.15–2.89) versus control subject and 2.71 (1.08–7.07) versus NC-HBV⁺ patients. The clinical phenotype specifically associated with type 2 diabetes was characterized by slightly older age; higher BMI, serum triglycerides, and blood pressure levels; and lower HDL cholesterol concentrations. Moreover, type 2 diabetic NC-HCV⁺ patients had a significantly lower BMI than type 2 diabetic control subjects and a slightly but significantly ($P < 0.05$) higher BMI than nondiabetic NC-HCV⁺ patients.

CONCLUSIONS— In the present study, we found a large excess of type 2 diabetes (12.6%) among NC-HCV⁺ patients compared with a sample of the general population or age-matched NC-HBV⁺ subjects. The RR of type 2 diabetes in NC-HCV⁺ was significantly higher than in control subjects or NC-HBV⁺ patients. The present series is a case-control study and not an epidemiological survey;

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Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

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—Clinical characteristics of HCV⁺ patients, HBV⁺ patients, and control subjects with or without diabetes

	Control subjects		HBV ⁺ patients		HCV ⁺ patients		P*		
	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	Diabetes	HCV ⁺	Diabetes × HCV ⁺
n	280	22	78	4	493	71			
Sex (F/M)	200/80	11/11	50/28	2/2	335/158	48/23	NS	NS	NS
Age (years)	60 ± 10	64 ± 10	57 ± 16	67 ± 6	61 ± 14	65 ± 10	0.0002	NS	NS
BMI (kg/m ²)	24.0 ± 2.5	29.9 ± 4.4	24.3 ± 2.3	27.2 ± 1.7	24.1 ± 3.3	25.7 ± 2.5	0.0001	0.0006	0.0002
Fasting plasma glucose (mmol/l)	5.0 ± 0.6	8.8 ± 3.0	5.1 ± 0.7	9.8 ± 3.1	5.1 ± 0.6	9.3 ± 4.1	0.0001	NS	NS
Serum total cholesterol (mmol/l)	6.0 ± 1.1	5.7 ± 1.0	5.2 ± 0.9	5.7 ± 0.8	4.4 ± 1.0	4.7 ± 1.1	NS	0.001	NS
Serum LDL cholesterol (mmol/l)	3.8 ± 1.0	3.6 ± 0.8	3.4 ± 0.9	3.8 ± 0.9	3.0 ± 1.5	3.2 ± 0.7	NS	0.04	NS
Serum HDL cholesterol (mmol/l)	1.5 ± 0.4	1.2 ± 0.3	1.4 ± 0.5	1 ± 0.1	1.3 ± 0.4	1.3 ± 0.4	0.005	NS	NS
Serum triglycerides (mmol/l)	1.4 ± 0.9	2.0 ± 1.4	1.4 ± 0.5	2.0 ± 0.3	1.5 ± 0.7	1.6 ± 0.6	0.02	NS	NS
Systolic blood pressure (mmHg)	131 ± 12	151 ± 14	131 ± 17	154 ± 10	130 ± 19	140 ± 19	0.0001	NS	NS
Diastolic blood pressure (mmHg)	80 ± 7	90 ± 10	79 ± 9	89 ± 8	81 ± 9	81 ± 10	0.001	NS	NS

Data are means ± SD. *P value for two-way ANOVA with diabetes and HCV⁺ as the factors and diabetes × HCV⁺ as the interaction term.

however, the prevalence of type 2 diabetes in control subjects (7%) was fully in the range of the reported age-adjusted prevalence rates for the Italian population (~4%) (10,14).

The current results closely agree with those of the only population-based survey to appear thus far in the literature (5), which reported a threefold increased odds ratio for type 2 diabetes in HCV⁺ patients >40 years of age in the general U.S. population. In that study, no distinction could be made between chronic hepatitis and cirrhosis because the clinical status of the HCV⁺ patients was not assessed. The prevalence of type 2 diabetes found in our NC-HCV⁺ patients is similar to that (17%) reported by Lecube et al. (9) and to that (14%) reported for HCV-related mixed cryoglobulinemia (12).

The current data suggest that HCV-related hepatitis is associated with type 2 diabetes at a stage when liver function is largely preserved. Interestingly, insulin resistance in nondiabetic HCV⁺ occurs already at an early stage in the course of HCV infection (15).

Of further interest in our analysis is the comparison between the clinical phenotype of hepatic and diabetic patients. Type 2 diabetes per se was associated with older age, overweight, dyslipidemia, and higher blood pressure levels, i.e., the "metabolic syndrome" phenotype commonly seen in these patients. In contrast,

nondiabetic NC-HCV⁺ patients were lean and had low LDL cholesterol levels. Low LDL cholesterol levels have been linked with HCV-induced hypobetalipoproteinemia as a consequence of a binding competition between the virus and the hepatic LDL receptor (16). Interestingly, our NC-HCV⁺ with type 2 diabetes had an intermediate clinical phenotype, as they were significantly leaner (25.7 vs. 29.7 kg/m²) and had lower LDL cholesterol concentrations (3.2 vs. 3.6 mmol/l) than HCV-negative diabetic patients (Table 1).

In conclusion, our study confirms an association of type 2 diabetes with HCV-related hepatitis and shows that HCV⁺ diabetic patients have a different clinical phenotype from classical type 2 diabetic subjects. In fact, type 2 diabetic NC-HCV⁺ patients present a significantly lower BMI than diabetic control subjects and a slightly but significantly higher BMI than nondiabetic NC-HCV⁺ patients.

Further investigation is needed to assess the biological basis for this association and to test whether antiviral therapy for HCV infection may prevent the appearance of type 2 diabetes.

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