# Diabetes Is the Main Factor Accounting for the High Ferritin Levels Detected in Chronic Hepatitis C Virus Infection

ALBERT LECUBE, MD[1]
CRISTINA HERNÁNDEZ, MD[1]
JOAN GENESCÀ, MD[2]
JOAN I. ESTEBAN, MD[2]
ROSEND JARDÍ, MD[3]
LYDIA GARCÍA, MD[3]
RAFAEL SIMÓ, MD[1]

**OBJECTIVE** — A high prevalence of diabetes has been reported in patients with hepatitis C virus (HCV) infection. Both diabetes and HCV infection are associated with high serum ferritin levels. Although HCV infection could be the main factor responsible for the high ferritin levels, it is also possible that diabetes rather than HCV infection might be a major contributor to the high ferritin levels observed in patients with HCV infection. The aim of this study was to investigate the contribution of diabetes to the high ferritin levels observed in HCV-infected patients with chronic hepatitis.

**RESEARCH DESIGN AND METHODS** — A total of 634 noncirrhotic individuals were prospectively recruited at a university hospital. According to the HCV antibody status and the presence of diabetes, the subjects were divided into four groups: group A (anti–HCV-positive diabetic patients, $n = 53$), group B (anti–HCV-negative diabetic patients, $n = 242$), group C (anti–HCV-positive nondiabetic patients, $n = 191$), and group D (anti–HCV-negative nondiabetic control subjects, $n = 148$). Multiple regression analyses were used to explore the variables independently related to ferritin levels.

**RESULTS** — Serum ferritin levels in group A were significantly higher than in the other groups (A > B, $P < 0.01$; A > C, $P < 0.001$; A > D, $P < 0.001$). Ferritin levels were higher in group B than in group D ($P = 0.001$). However, group C has ferritin values similar to those of group D. In multivariate analyses, diabetes but not HCV infection was independently related to serum ferritin concentrations.

**CONCLUSIONS** — Diabetes rather than HCV infection itself is the main factor associated with the increased ferritin levels detected in patients with HCV infection. Therefore, the presence of diabetes should be taken into account when iron metabolism is evaluated in HCV-infected patients.

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Increasing evidence exists suggesting an association between hepatitis C virus (HCV) infection and diabetes. In this regard, a high prevalence of HCV infection has been found among diabetic patients (1–3). Alternatively, a high prevalence of both diabetes and impaired fasting glucose has also been reported in HCV-infected patients in comparison with other liver diseases (4–8). The NHANES III (Third National Health and Nutrition Examination Survey) has shown that people >40 years of age with HCV infection were more than three times more likely to have type 2 diabetes than those without HCV infection (9). In addition, Mehta et al. (10) have reported that preexisting HCV infection may increase the risk of type 2 diabetes in individuals with recognized diabetes risk factors. Furthermore, Shintani et al. (11) have recently shown direct experimental evidence for the contribution of HCV in the development of insulin resistance using HCV core transgenic mice.

Type 2 diabetes is a condition frequently associated with elevated levels of serum ferritin (12,13). An association of high serum ferritin concentration and glucose intolerance and insulin resistance in healthy people has also been reported (14). Indeed, higher iron stores (reflected by an elevated ferritin concentration and a lower ratio of transferrin receptors to ferritin) are associated with an increased risk of type 2 diabetes in both healthy men (15) and women (16). Furthermore, a decrease in insulin resistance has been documented after iron depletion in type 2 diabetic patients (17,18). Given that several reports (19–22) have shown an increase of ferritin levels in patients with HCV infection, it could be speculated that iron stores are the link between HCV infection and diabetes. In fact, in previous cross-sectional or case-control studies, an association between elevated serum ferritin levels and the presence of diabetes in HCV-infected patients has been reported (23,24). However, although HCV infection could be the main factor responsible for the high ferritin levels, it is also possible that diabetes itself rather than HCV infection is the major contributor to this phenomenon. To shed light on this issue, we have determined serum ferritin levels in a large cohort of subjects, taking into account both HCV antibody status and the presence of diabetes.

From the [1]Diabetes Research Unit, Endocrinology Division, Hospital Universitari Vall d'Hebron, Barcelona, Spain; the [2]Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain; and the [3]Department of Biochemistry, Hospital Universitari Vall d'Hebron, Barcelona, Spain.

Address correspondence and reprint requests to Dr. Rafael Simó, Diabetes Research Unit, Endocrinology Division, Hospital General Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: rsimo@vhebron.net.

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**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGGT, γ-glutamyl transpeptidase; HCV, hepatitis C virus.

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

## RESEARCH DESIGN AND METHODS

— A total of 486 consecutive Caucasian patients with either type 2 diabetes and/or chronic HCV infection attending either the outpatient diabetes unit or the liver unit of a university hospital were prospectively recruited for the study from January 2001 to April 2002. Patients were divided in four groups according to their HCV antibody status and the presence of diabetes: anti–HCV-positive diabetic patients (group A, $n$ = 53), anti–HCV-negative type 2 diabetic patients (group B, $n$ = 242), and anti–HCV-positive nondiabetic patients (group C, $n$ = 191). A total of 148 anti–HCV-negative nondiabetic subjects with normal results of liver tests in whom routine analysis was performed served as the control group (group D). This group was obtained by including the spouses or relatives of patients from group C who agreed to participate.

The extra blood sample to determine the iron parameters was collected during routine analysis (generally in the immediate 4 months after recruitment). The exclusion criteria were as follows. *1*) Liver cirrhosis. *2*) Conditions other than diabetes and HCV infection that could influence either serum ferritin or glucose levels: premenopausal women; clinical evidence of hemorrhage in the preceding 6 months or serum ferritin levels <20 ng/ml in men or <10 ng/ml in women; treatment in the previous year with either iron, corticosteroids, or interferon; alcohol consumption >40 g/day; concomitant infection; and chronic diseases other than diabetes and hemochromatosis. (This condition was ruled out by either calculating the transferrin saturation index in groups B and D or by testing hemochromatosis gene mutations in HCV-infected patients [groups A and C].) *3*) Type 1 diabetes (history of diabetic ketoacidosis or age <30 years with insulin requirement) and secondary diabetes due to chronic pancreatitis or pancreatic tumor.

Liver cirrhosis was ruled out by liver biopsy performed within 18 months before inclusion (compensated patients) or by typical clinical features such as signs of portal hypertension (splenomegaly, ascites, and esophageal varices), hematologic evidence of hypersplenism, or biochemical evidence of hepatocellular failure. Liver biopsy and the other procedures performed (i.e., hepatic sonography or fibrogastroscopy) were not performed specifically for this study and were part of the routine care of the anti–HCV-positive patients. In the anti–HCV-positive patients (groups A and C, $n$ = 244), chronic hepatitis was diagnosed by liver biopsy in all patients in whom transaminase levels were elevated ($n$ = 186) and in 22 of 58 patients with normal transaminase levels. For the anti–HCV-positive patients with normal transaminase levels and no liver biopsy ($n$ = 36), we ensured that transaminase levels, liver function tests, and hepatic sonography results were persistently normal. In the anti–HCV-negative diabetic patients (group B), results of liver function tests were also 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 were used (25). 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.

All laboratory measurements were performed on fasting blood samples. The biochemical parameters analyzed included measurement of serum glucose, $HbA_{1c}$, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γGGT), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and creatinine. These parameters were measured by standard laboratory techniques used in clinical chemistry laboratories. Ferritin was mea-

**Table 1—*Main clinical and biochemical parameters of the patients included in the study***

| | Group A (anti–HCV-positive diabetic patients) | Group B (anti–HCV-negative diabetic patients) | Group C (anti–HCV-positive nondiabetic patients) | Group D (anti–HCV-negative nondiabetic control subjects) |
|---|---|---|---|---|
| *n* | 53 | 242 | 191 | 148 |
| Age (years) | 62.9 ± 9.8 | 64 ± 11 | 56 ± 13 | 55 ± 14 |
| Sex (% M/F) | 51/49 | 46.2/53.8 | 46.8/53.2 | 42.7/57.3 |
| BMI (kg/m$^2$) | 25.7 ± 4.1 | 31.5 ± 6.9 | 25.7 ± 4.3 | 28.1 ± 5.3 |
| Glucose (mmol/l) | 8.8 ± 3 | 9.3 ± 3.2 | 5.2 ± 0.5 | 5.3 ± 0.5 |
| $HbA_{1c}$ (%) | 8.4 ± 1.6 | 8.9 ± 1.6 | 5.5 ± 0.2 | 5.5 ± 0.3 |
| AST (IU/l) | 65 ± 40 | 19 ± 9 | 50 ± 41 | 22 ± 9 |
| ALT (IU/l) | 83 ± 60 | 23 ± 14 | 72 ± 71 | 25 ± 17 |
| γGGT (units/l) | 70 ± 49 | 33 ± 39 | 40 ± 49 | 39 ± 50 |
| Serum iron (μg/dl) | 123 ± 99 | 78 ± 30 | 106 ± 37 | 91.3 ± 32 |
| Transferrin (mg/dl) | 287 ± 54 | 235 ± 38 | 281 ± 48 | 247 ± 44 |
| Transferrin saturation index (%) | 38.7 ± 16 | 34.2 ± 14 | 38.1 ± 14 | 38.1 ± 16 |
| Hemoglobin (g/dl) | 14.3 ± 3.7 | 13.6 ± 1.3 | 14.3 ± 1.2 | 13.8 ± 1.4 |
| Hematocrit (%) | 42 ± 4.2 | 40.3 ± 3.7 | 42.2 ± 4 | 40.7 ± 3.7 |
| Serum ferritin* (ng/ml) | 184 (16–828) | 111 (10–831) | 85 (10–848) | 91 (11–959) |

Data are means ± SD or median (range). *Differences in serum ferritin levels between groups (Tukey's test): A > B ($P$ < 0.01), A > C ($P$ < 0.001), A > D ($P$ < 0.001), B > C ($P$ = 0.024), B > D ($P$ = 0.005), and C = D ($P$ = 0.9). Aside from serum iron, no differences in the other parameters of iron metabolism were observed among the groups.

**Table 2—*Comparison of clinical and laboratory variables taking into account the ferritin levels in anti–HCV-positive patients (groups A and C, n = 244) and after excluding diabetic patients (group C, n = 191)***

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | High ferritin (≥158 ng/ml) | Low ferritin (<158 ng/ml) | *P* | High ferritin ≥72 ng/ml | Low ferritin (<72 ng/ml) | *P* |
| Groups A and C | | | | | | |
| *n* (%) | 51 (41) | 72 (59) | | 61 (50) | 60 (50) | |
| Age (years) | 54 ± 13 | 53 ± 15 | 0.49 | 59 ± 11 | 56 ± 11 | 0.11 |
| BMI (kg/m$^2$) | 25.1 ± 2.8 | 24.7 ± 3.7 | 0.50 | 26.2 ± 4.5 | 25.1 ± 4.93 | 0.40 |
| Glucose (mmol/l) | 124 ± 47 | 100 ± 27 | 0.01 | 113 ± 48 | 98 ± 22 | 0.05 |
| Diabetes [*n* (%)] | 23 (45) | 10 (14) | 0.003 | 16 (26) | 4 (7) | 0.01 |
| Triglycerides (mg/dl) | 87 (36–238) | 83 (28–635) | 0.48 | 87 (37–625) | 88 (49–203) | 0.64 |
| AST (IU/l) | 50 (15–233) | 40 (11–138) | 0.014 | 40 (15–311) | 30 (14–148) | 0.03 |
| ALT (IU/l) | 64 (19–425) | 51 (10–349) | 0.015 | 46 (9–360) | 35 (11–289) | 0.03 |
| γGGT (units/l) | 44 (11–187) | 36 (11–126) | 0.13 | 24 (13–455) | 22 (6–77) | 0.09 |
| Group C | | | | | | |
| *n* (%) | 39 (43) | 51 (57) | — | 45 (45) | 56 (55) | — |
| Age (years) | 51 ± 13 | 49 ± 17 | 0.49 | 57 ± 11 | 55 ± 12 | 0.42 |
| BMI (kg/m$^2$) | 25.1 ± 2.9 | 24.3 ± 4.2 | 0.55 | 25.8 ± 3.8 | 25.2 ± 5.4 | 0.69 |
| Glucose (mmol/l) | 93 ± 8 | 90 ± 11 | 0.22 | 91 ± 9 | 93 ± 11 | 0.40 |
| Triglycerides (mg/dl) | 84 (36–191) | 84 (28–635) | 0.78 | 78 (46–162) | 85 (49–188) | 0.12 |
| AST (IU/l) | 38 (15–91) | 37 (11–138) | 0.20 | 33 (15–311) | 30 (15–141) | 0.27 |
| ALT (IU/l) | 59 (19–123) | 50 (18–349) | 0.23 | 36 (9–360) | 34 (15–289) | 0.29 |
| γGGT (units/l) | 42 (17–134) | 35 (11–109) | 0.14 | 20 (13–455 | 22 (6–67) | 0.22 |

Data are means ± SD or median (range) unless otherwise indicated.

sured by a turbidimetric fixed rate method (Olympus System Reagent; Olympus Diagnostica, Wendenstrabe, Hamburg, Germany). The normal values ranged from 20 to 300 ng/ml in adult men and from 10 to 20 ng/ml in adult women. Transferrin was measured by a turbidimetric end point method (Olympus System Reagent; Olympus Diagnostica). The normal values ranged from 200 to 360 mg/dl in both sexes. The coefficients of variation for intra-assay precision were 1.4–2.1%, and the total coefficient of variation was 1.5–2.1%. Serum iron was measured by a photometric color test for clinical chemistry analyzers (Olympus System Reagent; Olympus Diagnostica). The normal values ranged from 49 to 151 μg/dl in women and from 53 to 167 μg/dl in men. Transferrin saturation index was calculated using the formula serum iron × 70.9/transferrin.

Serological testing for anti-HCV was performed using a second-generation commercial enzyme immunoassay (Abbott Laboratories, Chicago, IL) according to the manufacturer's instructions. All anti–HCV-positive patients were HCV RNA-positive confirmed by RNA qualitative testing (Amplicor; Roche, Montclair, NJ).

Hemochromatosis gene mutations C282Y and H63D were screened using enzymatic digestion of PCR products encompassing the mutation sites as previously described (26). The restrictive enzymes used were *Rsa*I for the C282Y mutation and *Bcl*I for the H63D mutation.

### Statistical analysis

Before statistical analysis, normal distribution of the variances was evaluated using the Kolmogorov-Smirnov test. Descriptive results are expressed as median ± SD or as median (range), depending on whether the distribution was normal or skewed. Ferritin concentrations were log transformed to achieve a normal distribution. A high ferritin concentration was taken to correspond with the top third of values obtained in the control group (≥158 ng/ml for men and ≥72 ng/ml for women). Comparisons between groups were performed using ANOVA and Student's *t* tests for continuous variables and $\chi^2$ test for categorical variables. When multiple comparisons were performed, a Tukey's honestly significant difference test was used to avoid multiplicity errors.

To assess the variables independently related to serum ferritin in all individuals included in the study, as well as in anti–HCV-positive patients (groups A and C) and diabetic patients (groups A and B), stepwise multiple regression analyses were performed. Ferritin was considered the dependent variable, and the independent variables included in the analysis were age, sex, BMI, diabetes (yes/no), blood glucose, $HbA_{1c}$, HCV infection (yes/no), ALT, AST, γGGT, and triglycerides. All *P* values were based on a two-sided test of statistical significance. Significance was accepted at the level of $P < 0.05$. Statistical analyses were performed with the SSPS statistical package (SPSS, Chicago, IL).

**RESULTS** — The clinical and biochemical characteristics of each group are presented in Table 1. Distribution of sex was similar among groups. However, there was a significant difference among groups in age; individuals in groups A and B were older than individuals in groups C and D (A > C, $P < 0.001$; A > D, $P = 0.004$; B > C, $P < 0.001$; B > D, $P < 0.001$). By design, glucose and $HbA_{1c}$ levels were higher in groups A and B (diabetic patients) than in groups C and D (nondiabetic patients), and transaminase levels were higher in groups A and C

**Table 3—*Comparison of clinical and laboratory variables taking into account the ferritin levels in diabetic patients (groups A and B,* n = *295) and after excluding anti–HCV-infected patients (group B,* n = *242)***

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | High ferritin (≥158 ng/ml) | Low ferritin (<158 ng/ml) | *P* | High ferritin ≥72 ng/ml | Low ferritin (<72 ng/ml) | *P* |
| Groups A and B | | | | | | |
| *n* (%) | 79 (55) | 64 (45) | | 90 (59) | 62 (41) | |
| Age (years) | 60 ± 10 | 61 ± 11 | 0.60 | 66 ± 8 | 67 ± 11 | 0.15 |
| BMI (kg/m$^2$) | 28 ± 4 | 27 ± 4 | 0.11 | 31 ± 7 | 33 ± 8 | 0.11 |
| HCV infection [*n* (%)] | 23 (29) | 10 (16) | 0.04 | 16 (18) | 4 (6) | 0.03 |
| Glucose (mmol/l) | 156 ± 52 | 157 ± 60 | 0.91 | 175 ± 56 | 174 ± 65 | 0.46 |
| $HbA_{1c}$ (%) | 9.2 ± 0.7 | 8.9 ± 0.4 | 0.43 | 9.6 ± 2 | 9.7 ± 1.2 | 0.70 |
| Triglycerides (mg/dl) | 155 (57–1,300) | 140 (47–550) | 0.32 | 143 (37–625) | 139 (45–589) | 0.67 |
| AST (IU/l) | 21 (9–233) | 18 (11–111) | 0.12 | 19 (10–153) | 17 (10–97) | 0.001 |
| ALT (IU/l) | 31 (11–425) | 20 (9–124) | 0.000 | 23 (7–168) | 18 (7–56) | 0.000 |
| γGGT (units/l) | 30 (11–239) | 25 (9–360) | 0.04 | 22 (7–219) | 19 (8–77) | 0.03 |
| Group B | | | | | | |
| *n* (%) | 67 (61) | 43 (39) | | 74 (56) | 58 (44) | |
| Age (years) | 60 ± 10 | 62 ± 11 | 0.12 | 65 ± 8 | 67 ± 11 | 0.13 |
| BMI (kg/m$^2$) | 30 ± 4 | 27 ± 4 | 0.02 | 34 ± 7 | 34 ± 8 | 0.36 |
| Glucose (mmol/l) | 152 ± 55 | 164 ± 59 | 0.30 | 175 ± 55 | 176 ± 66 | 0.89 |
| $HbA_{1c}$ (%) | 9.3 ± 2 | 9.0 ± 2 | 0.43 | 9.8 ± 2 | 9.7 ± 1.5 | 0.68 |
| Triglycerides (mg/dl) | 175 (57–1,300) | 142 (57–435) | 0.08 | 147 (54–432) | 145 (45–589) | 0.39 |
| AST (IU/l) | 18 (9–46) | 17 (11–57) | 0.69 | 18 (10–86) | 17 (10–32) | 0.04 |
| ALT (IU/l) | 22 (11–107) | 18 (9–60) | 0.01 | 20 (7–82) | 17 (7–56) | 0.02 |
| γGGT (units/l) | 27 (12–239) | 23 (9–360) | 0.15 | 20 (7–206) | 19 (8–73) | 0.06 |

Data are means ± SD or median (range) unless otherwise indicated.

(HCV-infected patients) than in groups B and D (anti–HCV-negative patients).

Serum ferritin levels were significantly different among groups (ANOVA, $P < 0.01$). Ferritin levels in group A were higher than those in the other groups (Table 1). Diabetic patients (group B) showed higher ferritin levels than both anti–HCV-positive nondiabetic subjects (group C; $P < 0.001$) and the control group (group D; $P < 0.001$). However, ferritin levels in the anti–HCV-positive nondiabetic patients (group C) were similar to those in the control subjects (group D).

The relationship between ferritin (high or low levels) and the other variables considered in the study in anti–HCV-positive patients (groups A and C) and diabetic patients (groups A and B) are shown in Tables 2 and 3. In anti–HCV-positive patients, ferritin was related to the presence of diabetes and high levels of transaminases. However, when diabetic patients were excluded, the relationship between ferritin and transaminases disappeared (Table 2). In diabetic patients, ferritin was related to transaminases and the presence of HCV infection. The relationship between ferritin and transaminases persisted after excluding anti–HCV-positive patients (Table 3).

Multiple regression analyses showed that, apart from sex, ALT values and the presence of diabetes were independent predictors accounting for serum ferritin concentrations (Table 4). Notably, HCV infection was not related to serum ferritin concentrations either in all subjects or in diabetic patients.

**CONCLUSIONS** — A high serum ferritin concentration has been reported in patients with chronic HCV infection (19–22). However, the magnitude of this association has not been fully established because most available studies are uncontrolled. The reported controlled studies (27,28) are also difficult to interpret because they have not taken into account confounding factors such as sex distribution, alcohol consumption, severity of liver damage (cirrhosis versus chronic hepatitis), hemochromatosis gene mutations, or the presence of diabetes. In the present study, after considering the confounding factors mentioned above, we provide evidence that among HCV-infected patients, only anti–HCV-positive patients with diabetes have high ferritin concentrations. In fact, anti–HCV-positive patients without diabetes did not show higher ferritin concentrations than control subjects. In addition, we have observed higher serum ferritin levels in type 2 diabetic patients than in the control subjects. Furthermore, diabetes but not HCV infection was independently related to ferritin in multiple regression analyses. Taken together, our results suggest that the increase of serum ferritin reported in HCV infection could be related to the high prevalence of diabetes observed in these patients rather than to HCV infection itself.

The specific mechanisms that could lead to ferritin enhancement in type 2 diabetic patients remain to be elucidated. It is well known that chronic inflammatory diseases are associated with an increase in ferritin levels (29). In recent years, there has been a mounting body of evidence

**Table 4 —*Variables independently related to serum ferritin levels in all subjects (groups A–D), anti–HCV-positive patients (groups A and C), and diabetic patients (groups A and B)***

| | B | SE | β | *t* | *P* |
|---|---|---|---|---|---|
| All subjects* | | | | | |
| Sex (M/F) | −0.29 | 0.042 | −0.362 | −7.14 | <0.0001 |
| Diabetes (yes/no) | −0.26 | 0.048 | −0.288 | −5.36 | <0.0001 |
| Log ALT | 0.33 | 0.070 | 0.256 | 4.67 | <0.0001 |
| Constant | 2.32 | 0.126 | | 18.49 | <0.0001 |
| Anti–HCV-positive patients† | | | | | |
| Sex (M/F) | −0.29 | 0.064 | −0.350 | −4.65 | <0.0001 |
| Diabetes (yes/no) | −0.25 | 0.071 | −0.266 | −3.63 | <0.0001 |
| Log ALT | 0.24 | 0.109 | 0.168 | 2.20 | 0.028 |
| Constant | 2.49 | 0.277 | | 8.99 | <0.0001 |
| Diabetic patients‡ | | | | | |
| Sex (M/F) | −0.37 | 0.061 | −0.430 | −6.098 | <0.0001 |
| Log ALT | 0.47 | 0.112 | 0.299 | 4.240 | <0.0001 |
| Constant | 1.96 | 0.194 | | 10.114 | <0.0001 |

*$R^2 = 0.52$; variables also entered into multiple regression analysis but without statistical significance in the model: HCV infection (yes/no), age, BMI, log-AST, log γGGT, and log triglycerides. †$R^2 = 0.57$; variables also entered into multiple regression analysis but without statistical significance in the model: age, BMI, log AST, log γGGT, and log triglycerides. ‡$R^2 = 0.58$; variables also entered into multiple regression analysis but without statistical significance in the model: HCV infection (yes/no), age, BMI, log AST, log γGGT, glucose, $HbA_{1c}$, and log triglycerides.

that suggests a major role of inflammation in the etiopathogenesis of type 2 diabetes (30). In fact, inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 have been detected in significant amounts in patients with either insulin resistance syndrome or diabetes (31–33). However, hepatic iron stores have not been found to be increased in autopsy liver specimens from diabetic patients (34). Therefore, the high ferritin levels observed in diabetic patients could reflect either the extrahepatic iron stores or an inflammatory phenomenon as a part of an acute-phase reaction. To clarify this issue, we recently reported that serum ferritin levels are increased in type 2 diabetic patients in the absence of a reciprocal decrease of soluble transferrin receptors, thus suggesting that elevated ferritin levels in type 2 diabetic patients are mainly due to inflammatory mechanisms rather than to iron overload (35). In addition, Bugianesi et al. (36) have not found a relationship between serum ferritin levels and hepatic iron content in patients with nonalcoholic fatty liver disease.

Apart from diabetes, an independent association was found between ALT and ferritin levels in both the anti–HCV-positive patients and diabetic patients. In anti–HCV-positive patients, it might be possible that the relationship between ALT and ferritin levels could be attributed to iron-related hepatic damage. However, HCV infection is associated with significant elevations in serum markers of iron stores and with modest, if any, elevations of hepatic iron content (21,22). In addition, we have observed that when diabetic patients were excluded from anti–HCV-positive patients, there is no relationship between ALT and serum ferritin levels. Therefore, diabetes might be the link between high ferritin levels and ALT in HCV-infected patients. In this regard, it should be emphasized that fatty liver disease is closely related to insulin resistance (37,38), and it might be the reason for the association between high ALT and high ferritin levels.

The particularly high ferritin serum levels observed in our patients with both HCV infection and diabetes can probably be explained by the simultaneous occurrence of two inflammatory processes. Inflammatory mediators such as tumor necrosis factor-α and interleukin-6 have been detected in significant amounts, not only in subjects with insulin resistance or type 2 diabetes, but also in HCV-infected patients (39–41). Therefore, it could be postulated that HCV-infected patients with diabetes have a higher level of inflammation than HCV-infected patients without diabetes and, in consequence, higher serum ferritin levels. Moreover, it is also possible that as inflammatory mediator levels increase, the prevalence of diabetes in HCV-infected patients also increases.

In HCV-infected patients, the serum ferritin level is a predictive factor of severe hepatic fibrosis (42). An increased serum ferritin level has also been reported to predict nonresponse to treatment (interferon and ribavirin) in patients with chronic hepatitis C infection (43). On the other hand, a low serum level of ferritin conferred protection against persistent viremia (44). Complete responders to interferon-α 2b treatment also had lower ferritin values compared with the values for partial and nonresponders before starting therapy (45). In light of the findings in our study that an increased ferritin level in HCV infection is closely associated with diabetes, the interactions of diabetes with hepatic fibrosis, progression of iron deposition, and response to treatment in HCV infection deserve to be evaluated in future studies.

In conclusion, we provide evidence that anti–HCV-positive patients without diabetes did not show higher ferritin concentrations than control subjects. Therefore, the increase in ferritin levels detected in HCV patients is closely related to the presence of diabetes. In addition, diabetes should be taken into consideration when evaluating iron metabolism in HCV-infected patients. Further studies directly exploring proinflammatory mediators are necessary to investigate the nature and significance of the relationship between serum ferritin, insulin resistance, and HCV infection.

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