Association of Hepatitis C Virus Infection with Serum Iron Status: Analysis of Data from the Third National Health and Nutrition Examination Survey

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Background. There is growing evidence that mildly increased amounts of iron in the liver can increase hepatic injury, particularly if combined with other hepatotoxic factors, such as alcohol use, use of porphyrogenic drugs, or chronic viral hepatitis. In the present study, the association of hepatitis C virus (HCV) infection with serum measurements of iron status was assessed in the US population.

Methods. We analyzed data from a total of 14,462 participants in the Third National Health and Nutrition Examination Survey. We excluded subjects who were aged <12 years, subjects for whom measurements of serum levels of iron or ferritin or the results of liver function tests were missing, and subjects who had a serum transferrin saturation of $>$50% (to help exclude subjects with hemochromatosis).

Results. Mean serum levels of ferritin and iron (± standard error) were significantly higher among subjects with HCV infection (100 ± 3 ng/mL and 229 ± 17 µg/dL, respectively) than among subjects without liver disease (83 ± 0.3 ng/mL and 101 ± 2.1 µg/dL, respectively) (P<.0001). Serum levels of ferritin were directly and significantly correlated with serum levels of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transpeptidase (r = 0.25, r = 0.24, and r = 0.28, respectively; P<.0001), whereas platelet counts were inversely correlated with serum levels of ferritin (r = −0.12; P<.0001).

Conclusion. HCV infection is significantly associated with higher serum levels of ferritin and iron in the US population.

Chronic hepatitis C is a leading cause of liver-related morbidity and mortality in the United States and throughout the world. Current estimates indicate that 3.9 million people in the United States have been infected with hepatitis C virus (HCV) [1]. Despite progress in treating chronic hepatitis C with IFN or with IFN and ribavirin, most patients in the United States do not experience a sustained virological response with receipt of these therapies.

Iron is essential for life, but both severe iron deficiency and iron overload pose significant and potentially fatal health risks [2–6]. There is growing evidence that even mildly increased amounts of iron in the liver can be damaging, particularly if combined with other hepatotoxic factors, such as alcohol use, use of porphyrogenic drugs, or chronic viral hepatitis. Iron enhances the pathogenicity of microorganisms, adversely affects macrophages and lymphocytes, and enhances fibrogenic pathways, all of which may increase hepatic injury due to iron itself or due to the combination of iron with other factors. Iron may also be a cocarcinogen or a promoter of hepatocellular carcinoma, even in patients without hemochromatosis or cirrhosis [7].

Iron homeostasis may affect the clinical course of HCV infection. The findings of some studies have suggested that excess iron in the liver may predispose a patient to persistent viral infection and could have a negative effect on the response to IFN therapy [8–12]. In contrast, other studies have shown that patients with lower serum levels of ferritin, lower transferrin saturation values, and lower levels of iron in the liver have...
an improved response to IFN therapy [9, 13–15]. Several studies have demonstrated that the reduction of iron via therapeutic phlebotomy leads to improvements in serum levels of aminotransferases in patients with chronic hepatitis C and improves responses to standard IFN therapy [9, 13, 14, 16–18].

Iron may thus modulate the course of HCV infection via 3 mechanisms. First, iron interacts directly with cell-mediated immune pathways, thereby weakening Th1-mediated effector mechanisms, such as the formation of nitric oxide and the immune pathways, thereby weakening Th1-mediated effector mechanisms. First, iron interacts directly with cell-mediated immune pathways, thereby weakening Th1-mediated effector mechanisms, such as the formation of nitric oxide and the production of TNF-α [19, 20]. The weakening of IFN-γ activity and Th1-mediated effector mechanisms induces the expression of anti-inflammatory cytokines by Th2 cells, thereby creating an unfavorable condition for the fighting of infectious diseases, including HCV infection [21, 22]. Second, iron may worsen the clinical course of HCV infection by causing oxidant stress in nonparenchymal cells, which appears to cause irreversible mitochondrial derangement associated with the onset of hepatic fibrosis [23, 24]. Third, because iron is an essential nutrient for nearly all cells, the supply of iron may also affect the replication of HCV. This is supported by the finding that iron salts significantly increased HCV RNA levels in an HCV-infected human hepatocyte cell line [25].

Relatively few data have been published on serum levels of iron and ferritin and transferrin saturation (all of which are indicators of iron stores in the body) as putative risk factors for liver diseases, especially HCV infection, in the US population. Understanding the association of indicators of iron stores in the body with the risk for developing liver disease is important in the development of strategies to prevent morbidity associated with increased levels of iron or with liver disease. In the present study, we investigated the association of indicators of iron stores in the body with the development of HCV infection and liver diseases in a representative sample of the US population.

MATERIALS AND METHODS

Survey design and study sample. The Third National Health and Nutrition Examination Survey (NHANES III) was conducted by the National Center for Health Statistics (Hyattsville, MD). The procedures for data collection and analysis have been published elsewhere [26]. Participants in NHANES III represent the civilian, noninstitutionalized population of the United States. Laboratory studies evaluated liver function, presence of hepatitis viruses, nutritional biochemistry, and hematologic findings by use of standard techniques. Information regarding methodological variation of the assays was provided by Gunter and McQuillan [27]. Details about the methods used for the evaluation of serum levels of ferritin and iron and transferrin saturation have been reported by Looker et al. [28].

The primary source of data for the present study was NHANES III. Data on serum levels of iron, ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (GGTP); total iron-binding capacity; and transferrin saturation in the NHANES III database are based on measurements determined using blood samples drawn at a single time point. Because the indicators of serum iron stores change according to age (e.g., serum iron values generally are lower among individuals aged <17 years), sex (e.g., women often have increased serum iron levels after menopause), and race (e.g., the prevalence of hemochromatosis is higher among whites than among blacks or among individuals of other races), analyses of serum levels of iron and ferritin, total iron-binding capacity, and transferrin saturation were stratified by age, sex, and race.

We excluded subjects who were aged <12 years, because liver enzyme tests (i.e., for ALT, AST, and GGTP levels) were not performed for these individuals. Subjects of any age were excluded if they lacked data for serum levels of iron and ferritin, total iron-binding capacity, transferrin saturation, or liver enzyme test results. We also excluded subjects whose serum transferrin saturation was ≥50%, to help exclude subjects with phenotypically expressed hemochromatosis. The total number of subjects included in the present analysis was 14,462, of which 6696 (46.3%) were men and 7766 (53.7%) were women.

Definition of variables. Subjects who had elevated levels of any of the serum liver enzymes (i.e., ALT, AST, or GGTP levels of ≥40 U/L) were considered to have liver disease. Subjects who had elevated ALT, AST, or GGTP levels (i.e., levels of ≥40 U/L), a positive result of testing for HCV, and a negative result of testing for hepatitis B virus (HBV) were considered to have HCV infection. Subjects who had ALT, AST, and GGTP levels that were each <40 U/L and who lacked antibodies to HBV and HCV were considered to be healthy.

Assessment of potential confounding variables. Age, race, and sex affect levels of serum markers of iron stores and liver enzymes. These variables were selected a priori for inclusion in regression models as potential confounders, and data with regard to these variables were obtained during subject interviews and physical examinations. Race was categorized into 3 groups: non-Hispanic black, non-Hispanic white, and other. Age was categorized into 3 groups: 12–16 years, 17–46 years, and ≥46 years.

Statistical methods. Statistical analyses were performed using SAS software. We computed the prevalences of HCV infection and liver disease in the US population, as stratified by age, sex, and race. The frequencies were weighted according to the US population (per 1990 census data). For subjects with HCV infection and for healthy subjects, we computed the association of serum levels of iron and ferritin, total iron-binding capacity, and transferrin saturation. One-way analysis of vari-
Table 1. Prevalences of hepatitis C virus (HCV) infection and liver disease among 14,462 participants in NHANES III who represented the civilian, noninstitutionalized US population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of participants</th>
<th>No. (%) of participants With HCV infection</th>
<th>With liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6696</td>
<td>118 (1.8)a</td>
<td>1696 (25.3)a</td>
</tr>
<tr>
<td>Female</td>
<td>7766</td>
<td>70 (0.9)</td>
<td>1027 (13.2)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–16</td>
<td>1467</td>
<td>2 (0.1)</td>
<td>51 (3.5)</td>
</tr>
<tr>
<td>17–46</td>
<td>7069</td>
<td>122 (1.7)</td>
<td>1400 (19.8)</td>
</tr>
<tr>
<td>&gt;46</td>
<td>5926</td>
<td>64 (1.1)</td>
<td>1272 (21.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9480</td>
<td>85 (0.9)</td>
<td>1639 (17.3)</td>
</tr>
<tr>
<td>Black</td>
<td>4425</td>
<td>96 (2.2)b</td>
<td>981 (22.2)b</td>
</tr>
<tr>
<td>Other</td>
<td>557</td>
<td>7 (1.3)</td>
<td>103 (18.5)</td>
</tr>
<tr>
<td>Total</td>
<td>14,462</td>
<td>188 (1.3)</td>
<td>2723 (18.8)</td>
</tr>
</tbody>
</table>

NOTE. The frequencies, stratified by sex, age, and race, were weighted according to the US population (1990 census data). NHANES III, Third National Health and Nutrition Examination Survey.

Figure 1. Prevalences of hepatitis C virus (HCV) infection (A) and liver disease (B) among 14,462 participants in NHANES III, according to critical threshold cutoff values of >30 U/L, >40 U/L, or >50 U/L for serum levels of liver enzymes. The frequencies were weighted using 1990 census data for the US population. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, γ-glutamyl transpeptidase.

RESULTS

The prevalences of HCV infection and liver disease were estimated to be 1.3% and 18.8%, respectively, in the US population (table 1 and figure 1). The prevalence of HCV infection was ~2-fold higher among men than among women (P < .0001; table 1), was higher among blacks than among whites or among individuals of other races (2.2% vs. 0.9% and 1.3%, respectively; P < .0001), and was much higher among persons aged 17–46 years or aged >46 years than among persons aged 12–16 years (1.7% and 1.1% vs. 0.1%, respectively; P < .0001). The estimated prevalence of liver disease was also significantly higher among men than among women (25.3% vs. 13.2%; P < .0001), and it was significantly higher among persons aged 17–46 years or aged >46 years than among persons aged 12–16 years (19.8% and 21.5% vs. 3.5%, respectively; P < .0001). The prevalence of liver disease was higher among blacks than among whites or among individuals of other races (22.2% vs. 17.3% and 18.5%, respectively; P < .0001). Not surprisingly, the use of higher critical values (30 U/L, 40 U/L, or 50 U/L for each of the liver enzyme levels) produced lower prevalences of HCV infection (1.5%, 1.3%, and 1.2%, respectively; figure 1A) and liver disease (30.8%, 18.8%, and 12.9%, respectively; figure 1B). For subsequent analyses, 40 U/L was used as the cutoff value for all 3 liver enzyme levels, because it is the cutoff value in widest clinical use.

Mean serum levels of ferritin were markedly higher among subjects with HCV infection (mean, 229 ng/mL; 95% CI, 195–263 ng/mL) than among healthy subjects (mean, 101 ng/mL; 95% CI, 99–104 ng/mL; P < .0001) (figure 2). When we stratified subjects by age, sex, and race, we found that the mean serum concentrations of ferritin in all stratified subgroups of subjects with HCV infection were statistically higher than those in the group of healthy subjects (table 2). Interestingly, serum levels of ferritin were much higher among blacks with HCV infection than among whites with HCV infection (P < .0001) (table 2). Serum levels of ferritin among men were also significantly higher than those among women (P < .0001) (table 2).

Mean serum concentrations of iron were significantly higher among subjects with HCV infection (mean, 99.9 mg/dL; 95% CI, 89.0–110.8 mg/dL) than among healthy subjects (mean, 83.2 mg/dL; 95% CI, 80.4–86.0 mg/dL; P < .0001) (table 2).
CI, 94.2–105.6 μg/dL) than among healthy subjects (mean, 83.2 μg/dL; 95% CI, 82.6–83.8 μg/dL; P < .0001) (figure 2). Serum levels of iron in the stratified subgroups of subjects with HCV infection were significantly higher than those in the corresponding subgroups of healthy subjects for the majority of comparisons (table 3). Serum levels of iron among men, with or without HCV infection, were also significantly higher than such levels among women (P < .0001) (table 3). Mean serum total iron-binding capacity and mean transferrin saturation and transferrin saturation were higher among subjects who had HCV infection than among healthy subjects, but the differences were not statistically significant (P > .05) (figure 2).

We also analyzed the correlations of serum ferritin, serum iron, and transferrin saturation with levels of ALT, AST and GGTP and with platelet counts. Serum levels of ferritin were significantly and directly correlated with serum levels of ALT, AST, and GGTP (r = 0.25, r = 0.24, and r = 0.28, respectively; P < .0001 for all) (table 4). Similarly, serum levels of iron and transferrin saturation were significantly positively correlated with serum levels of ALT and AST, whereas platelet counts were inversely correlated with these measurements of iron status.

**DISCUSSION**

The major findings of this study are as follows: (1) liver disease is extraordinarily common in the US population (prevalence, 18.8%), and the prevalences of HCV infection and liver disease are significantly higher among men than among women and are higher among blacks than among whites or among individuals of other races; (2) subjects with HCV infection have significantly higher serum levels of ferritin and iron, compared with healthy subjects; (3) the serum levels of ferritin and iron are significantly higher among men and blacks than among women and whites, especially among subjects with HCV infection; and (4) the serum levels of ferritin and iron have significantly positive correlations with ALT, AST, and GGTP levels, whereas there is an inverse correlation with platelet counts.

The finding of abnormal results of liver function tests, particularly for ALT, AST, and GGTP levels, often triggers evaluations that lead to the diagnosis of liver disease. However, no
single enzyme test is specific for liver disease. Moreover, because serum liver enzyme levels can be normal in patients with HCV infection, near-normal serum ALT levels do not exclude the possibility of liver damage [29, 30]. Prati et al. [29] followed 6835 persons without anti-HCV antibodies and 209 persons with anti-HCV antibodies who were first-time blood donors. During a 6-month follow-up period, upper limits of serum ALT levels of 30 U/L (for men) and 19 U/L (for women) showed superior sensitivity in identifying subjects with HCV viremia. The authors advised a downward revision of normal limits for serum liver enzyme levels. We compared different cutoff values—namely, 30 U/L, 40 U/L, and 50 U/L—for ALT, AST, and GGTP serum levels of ALT. We compared different cutoff values—namely, 30 U/L, 40 U/L, and 50 U/L—for ALT, AST, and GGTP levels in the present study. As expected, the incidence of liver disease decreased as the cutoff levels for ALT, AST, and GGTP increased (i.e., prevalence was 31% at 30 U/L, 19% at 40 U/L, and 13% at 50 U/L) (figure 1B). An upper limit of normal of 40 U/L for serum ALT, AST, and GGTP levels is in wide clinical use; therefore, we used 40 U/L as our upper limit of normal in subsequent analyses.

Higher serum levels of iron were strongly associated with liver disease, especially HCV infection. Ruhl and Everhart [31] recently analyzed the associations of serum concentrations of iron and antioxidants with abnormal ALT activity, by use of NHANES III data but with data on HCV and HBV infection excluded, and they found that the risk for apparent liver injury was associated with higher transferrin saturation and serum iron values. In fact, higher values of transferrin saturation and serum levels of iron were consistently associated with elevated ALT, AST, or GGTP activity. This result extends earlier findings that suggested a role for iron in the development of nonhemochromatotic liver diseases [2–4, 7, 10, 15, 17, 18, 32–36]. Higher levels of iron have been associated with the failure of IFN treatment for chronic hepatitis C [2, 4, 10] and with the development of more-severe fibrosis in individuals with chronic hepatitis C [4, 24]. Rigamonti et al. [37] reported that serum levels of ferritin were directly correlated with the concentration of iron in the liver and with grading and staging scores for chronic hepatitis. Hofer et al. [38] recently reported that higher serum levels of ferritin at baseline, but not a higher serum transferrin saturation value or a higher concentration of iron in the liver, were predictors of a poor response to antiviral therapy in patients with chronic hepatitis C.

Although the pathogenesis of HCV infection remains imperfectly understood, one important factor is probably increased oxidative stress in hepatocytes. There is a compelling body of chemical, experimental, and clinical evidence that iron is toxic and fibrogenic by virtue of pathways involving oxy-

### Table 3. Association between hepatitis C virus (HCV) infection and serum levels of iron, as stratified by sex, age, and race among 11,655 participants in NHANES III who represented the civilian, noninstitutionalized US population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy subjects</th>
<th>HCV-infected subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>Mean serum levels of iron (95% CI), μg/dL</td>
<td>No. of subjects</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4833</td>
<td>90.2a (89.3–91.1)</td>
<td>118</td>
</tr>
<tr>
<td>Female</td>
<td>6634</td>
<td>78.2 (77.4–79.0)</td>
<td>70</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–16</td>
<td>1393</td>
<td>84.4 (82.6–86.2)</td>
<td>2</td>
</tr>
<tr>
<td>17–46</td>
<td>5593</td>
<td>85.5 (84.5–86.4)</td>
<td>122</td>
</tr>
<tr>
<td>&gt;46</td>
<td>4481</td>
<td>80.0 (79.2–80.9)</td>
<td>64</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7626</td>
<td>85.9 (85.2–86.7)</td>
<td>85</td>
</tr>
<tr>
<td>Black</td>
<td>3399</td>
<td>76.7 (75.6–77.8)</td>
<td>96</td>
</tr>
<tr>
<td>Other</td>
<td>442</td>
<td>87.1 (84.0–90.1)</td>
<td>7</td>
</tr>
</tbody>
</table>

**NOTE.** NHANES III, Third National Health and Nutrition Examination Survey.

a Differs from female sex, P < .0001.

### Table 4. Correlations of serum levels of ferritin and iron and transferrin saturation with liver enzyme levels and platelet counts among 14,462 participants in NHANES III who represented the civilian, noninstitutionalized US population.

<table>
<thead>
<tr>
<th>Level or count</th>
<th>Serum levels of ferritin</th>
<th>Serum levels of iron</th>
<th>Transferrin saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>ALT</td>
<td>0.25</td>
<td>&lt;.0001</td>
<td>0.14</td>
</tr>
<tr>
<td>AST</td>
<td>0.24</td>
<td>&lt;.0001</td>
<td>0.13</td>
</tr>
<tr>
<td>GGTP</td>
<td>0.28</td>
<td>&lt;.0001</td>
<td>0.10</td>
</tr>
<tr>
<td>Platelets</td>
<td>−0.12</td>
<td>&lt;.0001</td>
<td>−0.13</td>
</tr>
</tbody>
</table>

**NOTE.** ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, γ-glutamyl transpeptidase; NHANES III, Third National Health and Nutrition Examination Survey.
served sex differences in the incidence of HCV infection and liver disease. Our results raise the possibility that the observation of diseases that disproportionately affect blacks may provide clues as to whether elevated iron stores influence health.

The 3 possible explanations for these observations include: (1) iron overload facilitated viral replication in hepatocytes; (2) liver cells that contained the viruses tended to accumulate iron; and (3) iron overload may have altered the host response to viral infection. An important, still unresolved issue is whether the increases in levels of iron in serum or in the liver occur because of the chronic viral infection and are increased in more-severe forms of the disease, or whether a preexisting increase in iron predisposes patients to more-severe chronic hepatitis.

Ioannou et al. [43] recently reported that HCV-positive subjects who were black were 5.4 times more likely to have increased iron stores than were HCV-positive subjects who were not black. Compared with white patients, black patients with HCV infection have poorer response to antiviral treatment with IFN, pegylated IFN, or the combination of IFN and ribavirin [44–46]. We investigated whether there are differences between HCV-infected blacks and whites with regard to the presence of elevated iron stores, which is a predictor of poor response to IFN treatment [8, 10, 11]. Our results suggest that the increased prevalences of HCV infection and liver disease among blacks are associated with the observed increase in iron stores, as defined by elevations in serum levels of ferritin and iron and the transferrin saturation value, compared with that noted among whites and among individuals of other races. The relative contributions of nutritional factors versus genetic factors to increased iron accumulation in American blacks is unknown, but studies of South African blacks have provided evidence that both mechanisms are important [47, 48]. Increased dietary intake of iron probably is not responsible for the higher levels of ferritin in American blacks, because blacks typically consume less meat and ready-to-eat cereals (which are commonly supplemented with iron) than do whites [49]. A careful examination of diseases that disproportionately affect blacks may provide clues as to whether elevated iron stores influence health. For blacks, the rate of death due to all causes is ∼1.5 times that for whites [50].

Compared with women, men consistently have higher iron stores, as well as a significantly increased prevalence of HCV and liver disease. Our results raise the possibility that the observed sex differences in the incidence of HCV infection and liver disease may result, in part, from differences in serum levels of ferritin and iron.

With respect to HFE gene mutations as possible comorbid factors in chronic hepatitis C, an increased prevalence of the major C282Y mutation has been previously reported in patients with chronic hepatitis C [24, 51, 52]. Patients with mutations in the HFE gene, especially the major C282Y mutation, had higher mean serum levels of ferritin, more frequent stainable iron, and more-advanced fibrosis or cirrhosis at younger ages than did patients without these mutations. We and others recently reported that hepatic iron levels in patients with chronic hepatitis C were correlated with more-advanced hepatic fibrosis, higher serum levels of iron, and mutations of the HFE gene [4, 52–54]. However, in contrast to these results, Kazemi-Shirazi et al. [55] did not find evidence for more-advanced or precocious hepatic fibrosis in patients with mutations of the HFE gene. It is still uncertain whether higher iron levels cause more-severe liver disease or vice versa. These 2 possibilities are not mutually exclusive, and we think that both are probably correct.

One of the limitations of the present study was the use of elevated serum enzyme levels as indicators of liver disease. There are causes of increased enzyme levels that are unrelated to liver disease. Conversely, some patients with HCV infection do not have elevated enzyme levels. Another limitation was the inability to evaluate the severity of liver histological injury, because liver biopsies were not performed as part of NHANES III. In addition, we were unable to assess the possible role played by HFE gene mutations in causing iron overload or liver disease, because results of genetic tests have been kept strictly uncoupled from other patient data. To minimize the possible inclusion of subjects with hemochromatosis in the present analysis, we excluded subjects who had transferrin saturation values of >50%. Although there are diurnal variations in serum iron levels, it is unlikely that these variations influenced our results or conclusions, because the distributions of the time of day that blood samples were drawn were the same across all subject groups in NHANES III.

In conclusion, we have found that liver disease, as defined above, is common in the US population, especially among men aged ≥17 years. It is significantly more prevalent among blacks and men than among whites and women, chiefly because of the higher prevalence of HCV infection in the former groups. Liver diseases are associated with significantly higher serum levels of ferritin and iron and transferrin saturation values, even in the absence of hemochromatosis. Both iron overload and HCV infection increase oxidative stress, which causes or increases liver inflammation and fibrosis. The present analysis demonstrates that serum levels of ferritin and iron are directly correlated with serum levels of ALT, AST, and GGTP. However, a still unresolved issue is whether higher iron levels increase the risk for developing chronic hepatitis C, or, conversely,
whether liver damage causes increases in iron levels. Regardless of which occurs first, it is likely that increased iron levels contribute to the progression of hepatic injury and fibrosis.

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