Original Investigation

Screening for Hemochromatosis in Asymptomatic Subjects With or Without a Family History

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Background: Hemochromatosis in white subjects is mostly due to homozygosity for the common C282Y substitution in HFE. Although clinical symptoms are preventable by early detection of the genetic predisposition and prophylactic treatment, population screening is not currently advocated because of the discrepancy between the common mutation prevalence and apparently lower frequency of clinical disease. This study compared screening for hemochromatosis in subjects with or without a family history.

Methods: We assessed disease expression by clinical evaluation and liver biopsy in 672 essentially asymptomatic C282Y homozygous subjects identified by either family screening or health checks. We also observed a subgroup of untreated homozygotes with normal serum ferritin levels for up to 24 years.

Results: Prevalence of hepatic iron overload and fibrosis were comparable between the 2 groups. Disease-related conditions were more common in male subjects identified by health checks, but they were older. Hepatic iron overload (grades 2-4) was present in 56% and 34.5% of male and female subjects, respectively; hepatic fibrosis (stages 2-4) in 18.4% and 5.4%; and cirrhosis in 5.6% and 1.9%. Hepatic fibrosis and cirrhosis correlated significantly with the hepatic iron concentration, and except in cases of cirrhosis, there was a 7.5-fold reduction in the mean fibrosis score after phlebotomy. All subjects with cirrhosis were asymptomatic.

Conclusions: Screening for hemochromatosis in apparently healthy subjects homozygous for the C282Y mutation with or without a family history reveals comparable levels of hepatic iron overload and disease. Significant hepatic fibrosis is frequently found in asymptomatic subjects with hemochromatosis and, except when cirrhosis is present, is reversed by iron removal.

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HFE-ASSOCIATED HEREDITARY hemochromatosis is one of the most common autosomal recessive conditions in individuals of northern European ancestry. The prevalence of the responsible mutation (C282Y) is approximately 1 in 10 for heterozygotes and 1 in 200 for homozygotes.1 It is well established from cross-sectional population studies that between 60% and 80% of those at genetic risk will develop biochemical penetrance in the form of raised serum ferritin level and transferrin saturation.2,5 However, it is unclear how many people with biochemical penetrance will develop disease-related iron overload conditions such as cirrhosis and diabetes (clinical penetrance).3,6

Genetic-based population screening for this disease is not widely advocated because it has been suggested that disease burden is low.2 Others believe that it is an ideal disease to screen the population for because the complications are preventable.3 However, the true risk of disease for those with the genetic predisposition has not been elucidated since most large studies have been cross-sectional and have not used clinical evaluation with liver biopsy to assess hepatic disease.2,4,7,8

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Alternatives to genetic-based population screening have been advocated, including family screening of hemochromatosis probands9 and population-based phenotypic screening.10 Bulaj and colleagues9 found that a substantial number of homozygous relatives of patients with hemochromatosis had unrecognized dis-
ease, and these researchers emphasized the importance of family screening. Other studies have also favored this method of identifying affected individuals.11

Our present study aims to assess phenotypic expression of disease through clinical history, physical examination, serum iron indices, and liver biopsy findings in 672 apparently asymptomatic C282Y homozygotes, each identified through 1 of 2 different screening methods: (1) family screening of probands or (2) screening in primary medical practices. We also include long-term follow-up data on these individuals. Of the 672 homozygotes detected, 263 (39.1%) had significant hepatic iron loading (grades 3 or 4) and were thus at risk of long-term sequelae.6 Hepatic iron overload was as common in those identified by primary care physicians as in those identified by family screening. To our knowledge, this is the largest cohort of C282Y homozygotes yet described by clinical evaluation, hepatic histologic analysis, and longitudinal assessment.

**METHODS**

The study was approved by the ethics committee of each participating center. Written informed consent was obtained from all subjects.

**STUDY GROUPS**

**Group 1 (Family Screening)**

Screening for hemochromatosis was offered to relatives of 259 probands with proven C282Y-associated hemochromatosis. All available first-degree relatives were contacted and offered clinical assessment. Three relatives were previously diagnosed independently of their proband, but these were included in the analysis. A cohort of 401 subjects (200 male and 201 female) were identified as C282Y homozygotes and assessed.12,13 Probands were not included in further analysis for this study.

**Group 2 (Clinical Health Check)**

A total of 271 subjects (159 male and 112 female) were identified at health assessment examinations by primary care physicians either because they requested a routine health check (n=234 or 86.3%) or because they sought medical advice for minor ailments, specifically upper respiratory tract infections, headache, or backache (n=37 or 13.7%). Laboratory tests performed at the initial consultation included a standard multiple biochemical analysis, which included automated serum iron estimation. If the serum iron level was elevated, further investigations were carried out to establish or exclude C282Y homozygosity. Those subjects found to be homozygous were further evaluated for biochemical and clinical penetrance. All subjects were genotyped for HFE mutations,14 some retrospectively because their diagnoses were made before 1996 and were based on HLA linkage and family studies.15,16

**IRON STUDIES**

Analyses and reference ranges for liver function tests, transferrin saturation, serum ferritin levels, and iron concentrations were as previously described.15,16 Liver biopsy specimens were assessed for iron content by histologic staining. Iron stores were graded from 0 to 4, as detailed by Searle et al,17 and fibrosis was staged according to the scale first outlined by Scheuer18 (stage 4 equalling cirrhosis). The hepatic iron concentration (HIC) and hepatic iron index (HII) were also determined.19 Second liver biopsies were performed in 23 subjects after phlebotomy therapy was completed because of persistent elevation of liver enzymes or uncertainty about the presence of cirrhosis histologically.

**CLINICAL EVALUATION OF SUBJECTS**

All subjects were evaluated clinically by one of us (L.W.P., D.G.H., D.H.C., or M.L.B.) by means of a clinical history and physical examination, and relevant details including disease-related conditions were recorded. Alcohol consumption was assessed as previously described.16,19 A liver biopsy was performed in 350 subjects because of elevated serum ferritin levels (usually >500 µg/L), abnormal liver enzyme findings, hepaticomegaly, or a combination of these; 239 biopsies (68.3%) were performed for diagnostic purposes before HFE gene testing became available. The clinical and laboratory data were analyzed by 2 biostatisticians (D.M.P. and D.J.L.) who had no knowledge of the subjects. Liver biopsy specimens were evaluated by a pathologist (J.W.S.) who had no knowledge of clinical details, and the degree of fibrosis was assessed on reticulin stains in which intrahepatic iron was not discernible. Hepatitis B antigens and antibodies against hepatitis C virus were sought using the Axsym automated method (Abbott Laboratories, Abbott Park, Ill), and subjects testing positive for hepatitis B or C were excluded.

In a proportion of patients, we were able to assess the rate of iron accumulation in subjects with a rising serum ferritin level and also the histologic response to phlebotomy therapy. Subjects were divided into 2 pretreatment groups: those in whom the initial serum ferritin level was normal (nonexpressors, n=114) and those in whom it was elevated (expressors, n=110). Serum ferritin levels were observed serially in both groups until they showed a persistent rise or for periods up to 24 years. In the nonexpressors, if the level of serum ferritin rose above the normal range on at least 2 readings, phlebotomy was performed at weekly intervals until iron stores were depleted, as indicated by a transferrin saturation below 15% and/or a serum ferritin level of 20 µg/L or lower. Total mobilizable storage iron was calculated by the method first described by Walters et al.20 In the expressors, if the serum ferritin level rose progressively on at least 2 occasions, phlebotomy therapy was also performed, including calculation of total mobilizable storage iron. Those expressors without elevated serum alanine aminotransferase (ALT) levels (57 of 68 subjects) and those nonexpressors with serum ferritin levels that subsequently rose but without a rise in hepatic enzymes (54 of 55 subjects) were combined for statistical purposes. Of these 111 subjects, a total of 63 (25 male and 38 female) were observed for at least 6 months before phlebotomy was initiated (mean follow-up, 40.4 months; range of follow-up, 6.7-133.0 months). The progressive change in serum ferritin level was documented in these subjects.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using the SPSS software package, version 13.0 (SPSS Inc, Chicago, Ill). Age, alcohol intake, and transferrin saturation values were compared between groups using the t test. Group differences for serum ferritin levels, HIC, and HII were calculated using the Wilcoxon rank-sum test. Comparisons of serum ferritin concentrations (or other variables that were not normally distributed) were performed using Mann-Whitney nonparametric tests. The frequencies of morbidity or disease symptoms were compared using x² tests. In those sub-
DISEASE EXPRESSION

Table 1 classifies the homozygous subjects according to how they were identified. Biochemical expression was higher in men in group 2, who were also older and had higher levels of serum ALT. Disease-related conditions were also more common in men from group 2. There was no significant difference in mean age between women in groups 1 and 2, and although not statistically significant, the serum transaminase levels were higher in women in group 2. However, we found comparable levels of HIC, hepatic fibrosis, and cirrhosis in subjects from each group. There was no significant difference in alcohol consumption between the groups. Overall, biochemical expression of iron overload was present in 518 homozygotes (77%). Histologic hepatic iron overload (grades 2-4) was present in 56% of all male subjects (90.5% of males who underwent biopsy) and 34.5% of all females (84.4% of females who underwent biopsies). Stage 2 to 4 hepatic fibrosis was present in 18.4% and 5.4% of all male and female subjects, respectively (29.7% and 13.3%, respectively, of those who underwent biopsies), and cirrhosis was present in 5.6% of all males and 1.9% of all females. Of the 401 homozygotes in group 1, 54 (13.5%) had normal values for transferrin saturation.

The roles of age, HIC, and alcohol consumption as contributors to hepatic fibrosis and cirrhosis were assessed (Table 2). Both men and women with hepatic fibrosis and cirrhosis were older and had higher levels of serum ferritin, ALT, and HIC. The presence of fibrosis and cirrhosis when considered together was significantly associated with HIC and serum ferritin level for both men and women, but it did not correlate with alcohol intake. However, alcohol intake was higher in men with cirrhosis than in men without cirrhosis ($P<.01$). For women, the difference was not significant ($P = .81$).

All subjects with cirrhosis had HIC values greater than 200 µmol/g dry weight (dw) except for 3 men with heavy

<p>| Table 1. Clinical and Laboratory Findings in Homozygous Subjects |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects Identified Through Family Screening (Group 1)</th>
<th>Subjects Identified at Health Checks (Group 2)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 200)</td>
<td>Female (n = 201)</td>
<td>Male (n = 159)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>38 (10-75)</td>
<td>44 (6-86)</td>
<td>42 (17-73)</td>
</tr>
<tr>
<td>Alcohol consumption, mean (range)</td>
<td>38 (3-120)</td>
<td>17 (3-100)</td>
<td>38 (3-150)</td>
</tr>
<tr>
<td>median, g/d</td>
<td>TS, mean (range), %</td>
<td>72 (12-100)</td>
<td>64 (7-100)</td>
</tr>
<tr>
<td></td>
<td>SF, mean (10th-90th percentile range)</td>
<td>700</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>median, µg/L</td>
<td>474</td>
<td>1014 (213-2173)</td>
</tr>
<tr>
<td>Subjects with ALT elevation, No. (%)</td>
<td>47 (24)</td>
<td>13 (7)</td>
<td>61 (38)</td>
</tr>
<tr>
<td>Disease-related clinical conditions, No. (%) of subjects</td>
<td>49</td>
<td>20</td>
<td>58</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>13</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>29</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>At least 1 disease-related condition, No. (%) of subjects</td>
<td>49 (24.5)</td>
<td>20 (9.9)</td>
<td>58 (36.5)</td>
</tr>
<tr>
<td>Liver biopsy, No.</td>
<td>111</td>
<td>74</td>
<td>111</td>
</tr>
<tr>
<td>Grade 2 iron</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Grade 3 iron</td>
<td>41</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td>Grade 4 iron</td>
<td>41</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>HIC, mean (range) µmol/g dw</td>
<td>200 (9-766)</td>
<td>171 (6-700)</td>
<td>142</td>
</tr>
<tr>
<td>HIC, mean (range) µmol/g dw</td>
<td>200 (9-766)</td>
<td>171 (6-700)</td>
<td>142</td>
</tr>
<tr>
<td>Fibrosis stage 2 or 3, No. of subjects</td>
<td>5.2 (0.2-17.4)</td>
<td>4.4 (0.1-14.3)</td>
<td>4.2 (0.5-12.0)</td>
</tr>
<tr>
<td>Cirrhosis, No. of subjects</td>
<td>7</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; dw, dry weight; HIC, hepatic iron concentration; HII, hepatic iron index (HIC/age, y); NA, not applicable; SF, serum ferritin; TS, transferrin saturation.

*P values were derived from a test for group differences for age and transferrin saturation, from a Mann-Whitney nonparametric test for alcohol intake, and from the Wilcoxon rank-sum test for group differences for serum ferritin level, HIC, and HII. $P$ values were derived from either the Pearson $r^2$ or Fisher test for group differences for categorical variables.

†Male subjects in group 1 compared with males in group 2.
‡Female subjects in group 1 compared with females in group 2.
alcohol intake. When the 2 groups were combined, ROC curve analysis showed that a HIC of 236 μmol/g dw demonstrated optimal sensitivity (80%) and specificity (78%) in distinguishing patients with cirrhosis from those with no cirrhosis (area under the curve [AUC], 0.86; 95% confidence interval [CI], 0.8-0.91; P < .001) (Figure 1A). For serum ferritin, ROC curve analysis was performed, excluding subjects with alcohol ingestion of more than 60 g/d for men and more than 50 g/d for women and also excluding subjects with serum ALT levels greater than 60 U/L. The mean (SE) ages of these subjects at the end of the observation period were 35.2 (3.4) years for men and 46.7 (2.3) years for women. Correlation of serum ferritin levels and mobilizable body iron over a wide range of body iron stores in subjects who underwent phlebotomy therapy indicates that a rise of 1 μg/L of serum ferritin concentration represents 3.3 mg of storage iron (Figure 2). In the subjects observed, this equates to a mean body iron accumulation of 0.25 g/y in men and 0.21 g/y in women (ie, 0.68 and 0.57 mg/d, respectively). At this rate, if iron accumulation is linear, the time to reach a critical level of HIC for the development of cirrhosis (236 μmol/g dw) would be approximately 20.4 years after the serum ferritin rises to abnormal levels in men and 21 years in women (Figure 3).^{21-23}

**LONGITUDINAL ASSESSMENT**

Since no significant difference was detected between groups 1 and 2 with respect to HIC, the 2 groups were combined for analysis of longitudinal aspects of the effects of iron accumulation. In 114 subjects, the mean (SE) ages of 40.9 (3.4) years for men and 46.7 (2.3) years for women. Correlation of serum ferritin levels and mobilizable body iron over a wide range of body iron stores in subjects who underwent phlebotomy therapy indicates that a rise of 1 μg/L of serum ferritin concentration represents 3.3 mg of storage iron (Figure 2). In the subjects observed, this equates to a mean body iron accumulation of 0.25 g/y in men and 0.21 g/y in women (ie, 0.68 and 0.57 mg/d, respectively). At this rate, if iron accumulation is linear, the time to reach a critical level of HIC for the development of cirrhosis (236 μmol/g dw) would be approximately 20.4 years after the serum ferritin rises to abnormal levels in men and 21 years in women (Figure 3).^{21-23}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stage 1 or No Fibrosis (n = 146)</th>
<th>Stages 2-4 Fibrosis (n = 67)</th>
<th>P Value</th>
<th>Stage 1 or No Fibrosis (n = 102)</th>
<th>Stages 2-4 Fibrosis (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range) median, y</td>
<td>40 (12-73) 39</td>
<td>45 (15-75) 43</td>
<td>&lt;.01</td>
<td>42 (8-72) 41</td>
<td>50 (30-77) 47</td>
<td>.05</td>
</tr>
<tr>
<td>SF, mean (range) median, μg/L</td>
<td>927 (49-3516) 791</td>
<td>2164 (126-5500) 1905</td>
<td>&lt;.001</td>
<td>555 (30-3600) 416</td>
<td>1638 (323-3980) 1200</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALT, mean (range) median, U/L</td>
<td>56 (5-180) 47</td>
<td>92 (12-283) 72</td>
<td>&lt;.001</td>
<td>31 (10-81) 27</td>
<td>47 (20-77) 51</td>
<td>.02</td>
</tr>
<tr>
<td>Iron grade, No. of subjects</td>
<td>139</td>
<td>64</td>
<td>&lt;.001</td>
<td>95</td>
<td>16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIC, mean (range) median, μmol/g dw</td>
<td>168 (9-766) 131</td>
<td>247 (41-525) 246</td>
<td>&lt;.001</td>
<td>143 (1-700) 126</td>
<td>265 (75-518) 227</td>
<td>.02</td>
</tr>
<tr>
<td>HII, mean (range) median</td>
<td>4.3 (0.2-16) 3.8</td>
<td>5.8 (12-17.4) 5.2</td>
<td>&lt;.001</td>
<td>3.8 (3.1-14.3) 3.2</td>
<td>5.0 (1.5-87) 4.3</td>
<td>.17</td>
</tr>
<tr>
<td>Alcohol consumption, mean (range) median, g/d</td>
<td>36 (3-150) 20</td>
<td>45 (3-150) 30</td>
<td>.13</td>
<td>22 (5-100) 10</td>
<td>18 (5-50) 10</td>
<td>.85</td>
</tr>
</tbody>
</table>

**Table 2. Factors Relevant to the Development of Fibrosis or Cirrhosis**

Abbreviations: ALT, alanine aminotransferase; dw, dry weight; HIC, hepatic iron concentration; HII, hepatic iron index (HIC/age, y); NA, not applicable; SF, serum ferritin.

**RELATIONSHIP OF SERUM FERRITIN TO STAGE OF FIBROSIS**

Table 3 outlines the relationship of serum ferritin level to the stage of hepatic fibrosis in subjects, excluding those with serum ALT levels greater than 60 U/L. The mean age of the subjects increased with each increment of serum ferritin level to 2000 μg/L, and advanced fibrosis and cirrhosis were more common with high levels of serum ferritin. No case of cirrhosis was detected in subjects with a serum ferritin level of 1000 μg/L or lower.

**SUBJECTS WITH REPEATED LIVER BIOPSY**

Twenty-five subjects underwent a second liver biopsy after completion of phlebotomy to remove uncertainty about the presence of cirrhosis or to investigate the cause of cirrhosis.
pallently healthy subjects by primary care physicians. Furthermore, this is the largest study to date of clinical, biochemical, and histologic penetrance in C282Y homozygotes detected by screening and reports longitudinal data including a proportion of untreated individuals observed for up to 24 years.

We found comparable levels of HIC, hepatic fibrosis, and cirrhosis in subjects from each group (Table 1). Fibrosis of stage 2 or higher was present in 66 male subjects (18.4% of males overall and 29.7% of those undergoing biopsies) and 17 female subjects (5.4% of females overall and 13.3% of those undergoing biopsy). Cirrhosis was present in 5.6% of all men and 1.9% of all women, and all were asymptomatic. Thus, significant hepatic fibrosis is common in asymptomatic homozygous subjects, and clinically silent cirrhosis may also be present. In all subjects who underwent a second liver biopsy after phlebotomy therapy, the fibrosis score improved, except in cases of cirrhosis, and in 15 of 19 subjects, the fibrosis completely reversed. Niederau et al noted that fibrosis improved in 21 of 23 subjects who underwent repeated liver biopsies, but the specific staging of fibrosis was not documented.

Our findings in relatives are similar to those of Bulaj et al. In our study, 29.8% of men and 11.5% of women were found to have at least 1 disease-related condition. We acknowledge, however, that in the absence of controls, it is difficult to know what proportions of the arthropathy, diabetes, or other conditions are attributable to hemochromatosis. In addition, while the subjects with cirrhosis in our study were asymptomatic, they were at risk of complications, including variceal hemorrhage, hepatic decomposition, and hepatocellular carcinoma. Thus, cross-sectional studies may well have overlooked asymptomatic but potentially lethal disease that becomes evident only by clinical and liver biopsy evaluation.

There is compelling evidence from our findings and also from others that clinical features of hemochromatosis and hepatic fibrosis and cirrhosis are related to HIC. We found that the presence of fibrosis and cirrhosis correlated significantly with HIC but not with alcohol intake. However, alcohol intake was higher in men with cirrhosis than in men without cirrhosis, confirming the findings of Fletcher et al that excess alcohol ingestion increases the risk of extension of hepatic fibrosis to cirrhosis. The critical threshold of HIC leading to cirrhosis has been reported at a 7- to 10-fold increase above normal. In the present study HIC greater than 200 µmol/g dw (>5 times normal) was significantly associated with hepatic fibrosis and cirrhosis (excluding 3 men with heavy alcohol intake). Coexisting diseases, including porphyria cutanea tarda and steatohepatitis, may accelerate liver injury and fibrosis, but these were not analyzed systematically in our study.

In the present study there was nonexpression of disease in 17% of all subjects for periods up to 24 years. Similar observations have been made by others. It is possible that factors such as multiple blood donations and blood loss may account for this, but these were not compared in expressors vs nonexpressors. However, in our study, expressing male subjects were older than nonexpressors (P<.001) and had a higher alcohol intake (P<.05).

**Figure 1.** Receiver operating characteristic (ROC) curves. A, The ROC for hepatic iron concentration threshold distinguishes hemochromatosis patients with cirrhosis from those with no cirrhosis (area under the curve [AUC], 0.86; 95% confidence interval [CI], 0.80-0.91; P<.001). B, The ROC curve for serum ferritin threshold distinguishes hemochromatosis patients with cirrhosis from those with no cirrhosis (excluding all subjects with alcohol intake >60 g/d [men] and >50 g/d [women] and serum aminotransferase level >60 U/L [men and women]) (AUC, 0.96; 95% CI, 0.92-1.00; P<.001).

Population screening for hemochromatosis is not currently advocated owing to uncertainty about the natural history of the disease and the apparent discrepancy between the mutation frequency and clinical disease. For this reason, current interest is focused on optimal methods for detection of early disease. The present systematic study compares screening of family members of C282Y homozygous probands with screening of appar-
In the absence of inflammation, the best noninvasive marker of HIC is the serum ferritin level. We found that for each 1 µg/L rise in serum ferritin level, body iron content rose by approximately 3.3 mg. The notable difference between our findings with respect to serum ferritin levels over time and those of other recent studies may be explained by the effect of inflammation and hepatic injury, which were specifically analyzed in...
our study. Our estimate of the rate of iron accumulation with age indicates that the mean age of homozygotes whose health could be adversely affected by HIC greater than 236 µmol/g dw would be approximately 21 years after the hepatic iron stores begin to increase in both men and women. However, not all homozygous subjects who reach a HIC of 236 µmol/g dw develop cirrhosis, indicating the importance of other environmental and genetic factors that may modify tissue damage. These include mutations in other genes involved in iron metabolism, such as hepcidin,34-36 hemojuvelin,37 and other iron regulatory genes.38-40

In conclusion, we found that screening for hemochromatosis in the primary care setting and family screening reveal comparable levels of hepatic fibrosis and cirrhosis. Previously unidentified asymptomatic homozygotes are at a definite risk of iron overload–related hepatic fibrosis and cirrhosis, which, if diagnosed in the precirrhotic stage, can be reversed by iron removal by phlebotomy. Screening for hemochromatosis should not be confined to relatives of probands with disease.

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Table 3. Relationship of Serum Ferritin Level to Stage of Fibrosis in 256 Subjects*

<table>
<thead>
<tr>
<th>Serum Ferritin Level, µg/L</th>
<th>Age, Mean (SE), y</th>
<th>Fibrosis Stage, No. (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 (n = 93)</td>
<td>37.1 (1.6)</td>
<td>83 (89) 6 (7) 4 (4) 0 0</td>
</tr>
<tr>
<td>500-1000 (n = 95)</td>
<td>41.8 (1.3)</td>
<td>68 (72) 16 (17) 8 (8) 3 (3) 0</td>
</tr>
<tr>
<td>1001-2000 (n = 50)</td>
<td>46.0 (1.7)</td>
<td>25 (50) 8 (16) 11 (22) 4 (8) 0 0</td>
</tr>
<tr>
<td>2001-3000 (n = 11)</td>
<td>54.7 (3.4)</td>
<td>2 (18) 3 (27) 1 (9) 1 (9) 2 (7) 2 (4)</td>
</tr>
<tr>
<td>&gt;3000 (n = 7)</td>
<td>54.7 (3.4)</td>
<td>1 (14) 0 2 (29) 0 2 (36)</td>
</tr>
</tbody>
</table>

*Subjects with alanine aminotransferase levels higher than 60 U/L were excluded.

Figure 4. Reduction in fibrosis following phlebotomy therapy. Twenty-five subjects underwent a second liver biopsy after phlebotomy. Five subjects were excluded from analysis owing to significant alcohol intake (>60 g/d). In the remaining 20 subjects, the fibrosis score improved significantly following removal of iron by phlebotomy except where cirrhosis was present.
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