Serum Ferritin and Transferrin Saturation in Asians and Pacific Islanders

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Background: Asians and Pacific Islanders in the Hemochromatosis and Iron Overload Screening (HEIRS) Study had the highest prevalence of elevated serum ferritin (SF) and transferrin saturation (TS) levels, but to our knowledge, the reasons for this have not been investigated.

Methods: Using multiple linear regression, we compared TS and SF distributions for 42,720 Asian, Pacific Islander, and white HEIRS Study participants recruited through 5 field centers in North America who did not have HFE C282Y or H63D alleles.

Results: Compared with their white counterparts, Asian men had a 69-ng/mL (155-pmol/L) higher adjusted mean SF level and a 3% higher TS level (P<.001); Asian women had 23-ng/mL (52-pmol/L) higher adjusted mean SF level and a 3% higher TS level (P<.001). The mean TS level of Asian women was higher than that of Pacific Islander women, and the mean SF level of Pacific Islander men was significantly higher than that of white men. These differences remained significant after adjusting for self-reported history of diabetes or liver disease. Additional information for selected participants suggested that these differences are largely unrelated to mean corpuscular volume less than 80 fL, body mass index, or self-reported alcohol intake. Available liver biopsy and phlebotomy data indicated that iron overload is probably uncommon in Asian participants.

Conclusion: Higher TS and SF levels in persons of Asian or Pacific Island heritage may need to be interpreted differently than for whites, although the biological basis and clinical significance of higher levels among Asians and Pacific Islanders are unclear.

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AN ANALYSIS OF SCREENING data from the primary care–based Hemochromatosis and Iron Overload Screening (HEIRS) Study conducted in the United States and Canada showed that participants of Asian or Pacific Island heritage had elevated transferrin saturation (TS) and/or serum ferritin (SF) levels more often compared with other race/ethnic groups.1 The present study examines these differences further by comparing mean TS and SF levels of Asian, Pacific Islander, or white participants. We included only participants without HFE C282Y or H63D alleles to minimize the effect of common mutations of the hemochromatosis gene HFE.

METHODS

The HEIRS Study's target population was primary care patients. Participants completed a questionnaire that included race and Hispanic/Latino heritage and gave blood specimens collected without respect to fasting status. Participants with elevated TS and SF levels or homozygosity for HFE C282Y (cases) were invited to participate in a limited clinical examination. For individuals with persistently elevated SF levels, information on therapeutic phlebotomy and liver biopsies that were performed as part of clinical care was collected. A comparison group of individuals who had TS and SF levels within the mid-50th percentile of sex-specific TS and SF distributions and neither an HFE C282Y nor H63D allele (controls) were invited to participate in the same examination. Details about study design, recruitment, data collection, and laboratory methods are available elsewhere.1 A list of HEIRS Study institutions appears in a box at the end of this article.
STUDY POPULATION

Participants who reported hearing about the HEIRS Study exclusively from a family member, reported having been previously diagnosed as having hemochromatosis or iron overload, had an HFE C282Y or H63D allele, or had incomplete TS, SF, or HFE genotype data were excluded from analyses. We included participants who marked a combination of Asian, white, or Pacific Island heritage and formed 3 groups: (1) any Pacific Island heritage (386 men and 662 women); (2) only Asian heritage (4697 men and 6996 women); and (3) only white heritage (11 255 men and 18 742 women). Median ages (women/men) were 50/52 years for Asians; 52/55 for Pacific Islanders; and 51/54 for whites. Most Asian participants were recruited at the following 3 field centers: Kaiser Permanente in Hawaii (58% Japanese, 22% Chinese, and 17% Filipino [categories not exclusive]); London Health Sciences Centre in Toronto, Ontario (70% Chinese and 20% Vietnamese); and University of California, Irvine (90% Vietnamese).

STATISTICAL ANALYSES

Multiple linear regression analyses assessed differences in mean TS and SF levels among Asians, Pacific Islanders, and whites. A natural log (ln) transformation was applied to SF levels. We stratified by sex, included age and field center as covariates to account for potential confounding, and included an interaction term for field center and race/ethnicity to allow for variation among field centers. We present observed means and standard deviations and least square means based on regression models. Additional models included self-reported diabetes or liver disease. The differences were small. Asian men and women had significantly higher mean TS levels compared with Pacific Islander men and women with an MCV less than 80 fL, which is similar to controls. When analyzed by sex, there was a significant difference between Asians and whites. Some of these differences were relatively large, and significant differences remained after adjusting for history of diabetes and liver disease. Asian and Pacific Islander men and women had significantly higher mean SF levels compared with white men and women at the 2 field centers with larger numbers of Asians and Pacific Islanders (P < .001). Asians differed significantly from whites at the London Health Sciences Centre (P < .001).

MEAN CORPUSCULAR VOLUME

Among cases, Asians more often had an MCV less than 80 fL compared with whites (7.6% vs 1.5% for women and 6.1% vs 1.8% for men). No Pacific Islander cases or controls had an MCV less than 80 fL. Asians with an MCV less than 80 fL had higher mean screening SF levels compared with other Asians. However, 9% of Asian female controls had an MCV less than 80 fL, which is similar to that among female cases. No Asian male controls had an MCV less than 80 fL.

ALCOHOL INTAKE AND BMI

Among cases, Asian men and women had a lower mean BMI (25 and 24, respectively) compared with their white counterparts.

RESULTS

TRANSFERRIN SATURATION

Asians had the highest mean TS level, which differed significantly from the mean TS levels in Pacific Islander and white women and in white men (Table), even after adjusting for history of diabetes and liver disease. The differences were small. Asian men and women had significantly higher mean TS levels compared with Pacific Islander and white men and women at field centers with larger numbers of Asians and Pacific Islanders (Kaiser Permanente and University of California, Irvine) (P < .001 for all comparisons, except P < .02 for Asians compared with Pacific Islanders at University of California, Irvine). Asians differed significantly from whites at the London Health Sciences Centre (P < .001).

SERUM FERRITIN

Among men, Asians and Pacific Islanders had higher mean SF levels compared with whites (Table). Among women, there was a significant difference between Asians and whites. Some of these differences were relatively large, and significant differences remained after adjusting for history of diabetes and liver disease. Asian and Pacific Islander men and women had significantly higher mean SF levels compared with white men and women at the 2 field centers with larger numbers of Asians and Pacific Islanders (P < .001). Asians differed significantly from whites at the London Health Sciences Centre (P < .001).

Table. Mean Transferrin Saturation (TS) and Serum Ferritin (SF) Levels, Stratified by Sex

<table>
<thead>
<tr>
<th>Sex and Race/Ethnicity</th>
<th>Observed Mean ± SD</th>
<th>Adjusted Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n = 26374)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>30.3 ± 11.5</td>
<td>28.8 (27.9-29.6)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>149.8 ± 188.2</td>
<td>90.6 (84.4-97.4)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>25.4 ± 10.2</td>
<td>23.4 (20.0-26.8)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>171.4 ± 178.7</td>
<td>82.9 (62.9-109.2)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>25.6 ± 10.6</td>
<td>25.5 (25.1-25.8)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>87.5 ± 93.7</td>
<td>68.0 (66.1-70.1)</td>
</tr>
<tr>
<td><strong>Men (n = 16309)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>36.1 ± 12.6</td>
<td>33.6 (32.5-34.7)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>334.1 ± 279.5</td>
<td>207.4 (191.6-223.9)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>31.0 ± 11.5</td>
<td>31.9 (26.7-37.1)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>390.4 ± 338.3</td>
<td>270.0 (185.5-386.6)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS, %</td>
<td>30.6 ± 11.0</td>
<td>30.4 (29.9-30.9)</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>194.2 ± 174.6</td>
<td>138.8 (134.4-143.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SF, serum ferritin; TF, transferrin saturation.

SI conversion factor: To convert SF to picomoles per liter, multiply by 2.247.

*In addition to race/ethnicity, analytic models included age, field center, and field center by race/ethnicity interaction; adjusted mean is a least squares mean. Analyses for SF were performed using natural log (ln) SF.†TS: Asians differed significantly from Pacific Islanders and whites (P < .002 and P < .001, respectively). SF: Asians differed significantly from whites (P < .001).
‡TS: Asians differed significantly from whites (P < .001). SF: Asians and Pacific Islanders differed significantly from whites (P < .001 for both).
(28 and 29, respectively) and Pacific Islander (31 and 31, respectively) counterparts. The same pattern was observed for controls. Body mass index was not correlated with SF levels in any group. Asians and Pacific Islanders had lower mean alcohol intake compared with whites, stratified by sex and case-control status. The correlation between screening SF level and alcohol intake was statistically significant only for Pacific Islander male cases and Pacific Islander female controls (P<.05).

**THERAPEUTIC PHLEBOTOMY**

The median amount of iron removed was 1.86 g for 26 Asians and 1.66 g for 7 whites, which was not significantly different. One Pacific Islander received phlebotomy treatment but did not achieve iron depletion.

Iron overload can cause serious health problems through parenchymal damage to organs, but primary iron overload appears to be rare in Asian populations. Asians and Pacific Islanders, however, may have persistently higher TS or SF levels compared with whites, affecting interpretation of screening results. In a retrospective study of 65 Southeast Asian patients referred to subspecialists for evaluation of hyperferritinaemia, 32 had identifiable secondary causes, 4 had clinical or biopsy-proven iron overload, and 29 had isolated hyperferritinaemia. The limited information about screening for iron overload among Asians or Pacific Islanders includes reports that Asian men had elevated TS values as often as whites and that mean TS levels of Asian men and women were similar to those of whites. Individuals visiting a health promotion center in Seoul, Korea, had higher mean TS levels than the levels reported for similarly selected Australian and African American populations, consistent with previous and the present HEIRS Study findings. Among participants who do not have an HFE C282Y or H63D allele, Asians had significantly higher mean TS level compared with whites; Asian women had a significantly higher mean TS level compared with Pacific Islanders, and Pacific Island men had a significantly higher mean SF level compared with whites. These differences were especially pronounced for SF. Differences were not explained by the effects of age, field center, or prevalence of self-reported history of diabetes or liver disease. Consistency across field centers suggests that these results are relevant to people of Chinese, Filipino, Japanese, and Vietnamese heritage living in North America.

Possible interpretations include the higher frequency of comorbidities or risk factors for elevated SF levels or iron overload among people of Asian or Pacific Island heritage and higher “normal” values for TS and SF levels in Asian populations and SF level in Pacific Island populations. Liver disorders can cause elevated SF concentrations, are common, and have different prevalences in Asians, whites, and Pacific Islanders. Self-reported diabetes and liver disease did not account for observed racial/ethnic differences in mean TS and SF levels, but self-reported diagnoses do not include undiagnosed liver disease and diabetes. Thus, we cannot completely account for possible differences in the prevalence of underlying disease among racial/ethnic groups. Among those participating in a follow-up examination, we found no consistent evidence that differences in SF levels among racial/ethnic groups can be explained by BMI or alcohol intake.

Some inherited hemoglobin disorders are associated with iron loading and have different prevalences in various racial/ethnic groups. We examined MCV less than 80 fl (as a surrogate indicator of thalassemia trait) in participants who completed a follow-up examination. Asian men with an MCV less than 80 fl had a higher mean SF level compared with Asian men with higher MCV values. A higher prevalence of thalassemia trait may partly explain higher mean SF levels in Asian men.

There was little evidence of significant iron overload among Asians as assessed by quantitative phlebotomy. Among 8 Asian participants who had liver iron concentrations measured in liver biopsy specimens, 3 had increased liver iron concentrations (reference range, 0-36 mMol/g). These observations indicate that there are innate biological differences in TS and SF levels across racial/ethnic groups and that TS and SF levels in persons of Asian or Pacific Island heritage must be interpreted differently than those in whites. Race/ethnicity-specific reference ranges for TS and SF levels and more studies to identify a possible genetic basis for higher TS and SF levels among Asians and Pacific Islanders are needed.

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**Author Contributions:** Dr Harris had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design: Harris, C. McLaren, Reboussin, Gordeuk, Barton,*
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