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CLINICAL RESEARCH STUDY

African Americans at Risk for Increased Iron Stores or Liver Disease

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ABSTRACT

PURPOSE: We sought to determine the prevalence of elevated measures of iron status in African Americans and whether the combination of serum ferritin concentration >200 μg/L for women or >300 μg/L for men and transferrin saturation in the highest quartile represents increased likelihood of mutation of *HFE*, self-reported iron overload or self-reported liver disease.

SUBJECTS AND METHODS: A cross-sectional observational study of 27,224 African Americans ≥25 years of age recruited in a primary care setting was conducted as part of the multi-center, multi-ethnic Hemochromatosis and Iron Overload Screening (HEIRS) Study. Measurements included serum ferritin concentration, transferrin saturation, testing for *HFE* C282Y and H63D, and self-reported iron overload and liver disease.

RESULTS: Serum ferritin concentration >200 μg/L for women or >300 μg/L for men occurred in 5263 (19.3%) of African Americans, while serum ferritin concentration in this range with highest-quartile transferrin saturation (>29% women; >35% men) occurred in 1837 (6.7%). Adjusted odds of *HFE* mutation (1.76 women, 1.67 men), self-reported iron overload (1.97 women, 2.88 men), or self-reported liver disease (5.18 women, 3.73 men) were greater with elevated serum ferritin concentration and highest-quartile transferrin saturation than with nonelevated serum ferritin concentration (each $P < .05$).

CONCLUSIONS: Serum ferritin concentration >200 μg/L for women or >300 μg/L for men in combination with transferrin saturation >29% for women or >35% for men occurs in approximately 7% of adult African American primary care patients. Patients with this combination of iron test results should be evaluated for increased body iron stores or liver disease.

KEYWORDS: African Americans; Serum ferritin; Transferrin saturation; *HFE*; Liver disease; Increased iron stores

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Increased iron stores attributable to dietary and possibly heritable factors occur in approximately 10% of rural adults in sub-Saharan Africa,[1,2] but few cases of primary increases in body iron stores have been reported in African Americans.[3,4] Nonetheless, autopsy studies suggest that an increase in hepatic iron is a fairly common finding in African Americans.[5,6] Most Africans and African Americans with increased iron stores do not have *HFE* mutations that are common in whites with hemochromatosis,[5,7-9] and the prevalence of *HFE* C282Y homozygosity is approximately 14 per 100,000 among African American primary care patients.[10]

Increased iron stores may lead to multisystem organ dysfunction, contribute to the severity of viral hepatitis, or increase the risk for certain infections and malignancies.[3,11] Increased iron stores are often suspected when there is an unexplained elevation in serum ferritin concentration and transferrin saturation. Elevations in these measures of iron status are not in themselves sufficient to confirm a diagnosis of increased iron stores, for this combination is frequently seen in liver disease without iron overload. In the multicenter HEmochromatosis and IRon Overload Screening (HEIRS) Study in the US and Canada, more than 100,000 participants, of whom more than 27,000 were self-identified as African Americans, were tested for serum ferritin concentration, transferrin saturation, and *HFE* mutations, and questioned regarding health conditions including iron overload and liver disease.

Infectious and other inflammatory processes, hepatic disorders such as alcoholic and viral hepatitis and nonalcoholic steatohepatitis (NASH), and increased body iron stores resulting from multiple blood transfusions, *HFE* mutations, or other primary processes are all potential causes of increases in serum ferritin concentrations.[12-19] Inflammatory processes are typically characterized by reduced serum iron concentration and transferrin saturation in association with increased serum ferritin concentration.[18] On the other hand, patients with elevated iron stores or hepatic disorders tend to have transferrin saturations above the population mean in association with increased serum ferritin concentration.[19,20] We therefore reasoned that assessing serum ferritin concentration in the context of the accompanying transferrin saturation would be useful in developing certain broad categories of potential causes for serum ferritin elevation. Specifically, we hypothesized that serum ferritin concentration above the upper limit of the reference range in association with transferrin saturation in the upper population quartile would represent increased likelihood of *HFE* mutation, self-reported iron overload, or self-reported liver disease. We also hypothesized that serum ferritin concentration above the upper limit of the reference range in association with transferrin saturation in the lower population quartile would represent increased likelihood of self-reported inflammatory processes.

CLINICAL SIGNIFICANCE

- Elevated serum ferritin (>200 μg/L women, >300 μg/L men) in combination with highest quartile transferrin saturation (>29% women, >35% men) occurred in 7% of 27,224 African American primary care patients.
- This combination was associated with significantly increased odds of *HFE* mutation, self-reported iron overload, and self-reported liver disease.
- African American patients with elevated ferritin and highest quartile transferrin saturation should be screened for increased iron stores and liver disease.

STUDY PARTICIPANTS AND METHODS

Study Approval

The local Institutional Review Board of each field center approved the study protocol, which is described in detail elsewhere,[21] and written informed consent was obtained from each participant.

Selection of Study Subjects

Participants 25 years of age or older were recruited during the interval of February 2001 to March 2003 from public and private primary care offices and ambulatory clinics (Howard University, Washington, DC; University of Alabama at Birmingham; and University of California, Irvine), from a health maintenance organization (Kaiser Permanente Northwest in Portland, Oregon and Kaiser Permanente Hawaii), and from diagnostic blood collection centers (MDS Laboratories, London, Ontario, and Dynacare Laboratories, Richmond Hill, Ontario, Canada) associated with the 5 HEIRS Study field centers. These facilities serve ethnically and socioeconomically diverse primary care patients. Other adult volunteers, such as family members or friends accompanying a patient, were also eligible to participate.[21]

At the screening visit, HEIRS Study participants completed a questionnaire that included questions about race/ethnicity.[21] Of the 101,168 participants with complete transferrin saturation, serum ferritin concentration, and *HFE* mutation results, those who identified themselves only as African American or black, hereafter referred to as African Americans, were selected for this analysis. Participants who also reported Hispanic race/ethnicity or 2 or more race/ethnicity groups were not included in this analysis. The questionnaire also asked whether participants had ever been diagnosed with any or all of the following conditions: iron overload or hemochromatosis, arthritis, diabetes mellitus, liver disease or liver cancer, heart failure, and fertility problems or impotence. The options for each category were "yes," "no," or "not sure." Blood samples were obtained from participants to measure transferrin saturation and serum ferritin concentration and to analyze for *HFE* C282Y and H63D mutations.