Insulin Resistance and Metabolic Syndrome: Clinical and Laboratory Associations in African Americans Without Diabetes in the Hemochromatosis and Iron Overload Screening Study

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Abstract

Background: We sought to determine associations with insulin resistance (IR) and metabolic syndrome (MetS) in African Americans.

Methods: We studied African American adults without diabetes in a postscreening examination. Participants included Cases: transferrin saturation (TS) >50% and serum ferritin (SF) >300 µg/L (M), and TS >45% and SF >200 µg/L (F), regardless of *HFE* genotype; and Controls: TS/SF 25th to 75th percentiles and *HFE* wt/wt (wild type). We excluded participants with fasting <8 h; fasting glucose >126 mg/dL; hepatitis B or C; cirrhosis; pregnancy; or incomplete datasets. We analyzed age; sex; Case/Control; body mass index (BMI); systolic and diastolic blood pressures; neutrophils; lymphocytes; alanine aminotransferase; aspartate aminotransferase; elevated C-reactive protein (CRP >0.5 mg/L); TS; and SF. We computed homeostasis model assessment of insulin resistance (HOMA-IR) using fasting serum glucose and insulin, and defined IR as HOMA-IR fourth quartile (≥ 2.42).

Results: There were 312 Cases and 86 Controls (56.3% men). Ninety-one percent had *HFE* wt/wt. None had *HFE* p.C282Y. A significant increasing trend across HOMA-IR quartiles was observed for BMI only. Multivariable regression on HOMA-IR revealed significant positive associations: age; BMI; lymphocytes; SF; and CRP >0.5 mg/L; and significant negative associations: neutrophils and TS. Logistic regression on IR revealed BMI [odds ratio (OR) 1.3 (95% confidence interval 1.2–1.4)] and CRP >0.5 mg/L [OR 2.7 (1.2–6.3)]. Fourteen participants (3.5%) had MetS. Logistic regression on MetS revealed one association: IR [OR 7.4 (2.1–25.2)].

Conclusions: In African Americans without diabetes, IR was associated with BMI and CRP >0.5 mg/L, after adjustment for other variables. MetS was associated with IR alone.

Keywords: body mass index, C-reactive protein, *HFE*, HOMA-IR, serum ferritin

Introduction

INSULIN RESISTANCE (IR) and metabolic syndrome (MetS) are risk factors for diabetes mellitus (diabetes), the prevalence and complications of which are significantly greater in African Americans than whites.¹ In participants without diabetes in the National Health and Nutrition Examination Survey (NHANES; 1988–1994), the proportion of African Americans with IR defined as homeostasis model assessment of insulin resistance (HOMA-IR) fourth quartile was significantly greater than that of whites.² In a

community-based study of metropolitan Atlanta residents, the prevalence of MetS was significantly greater in African Americans than whites.³

The aim of this study was to determine significant clinical and laboratory associations with IR (HOMA-IR fourth quartile)⁴ and MetS⁵ in a cohort of 398 African Americans without diabetes who attended a postscreening Clinical Examination (CE) of the Hemochromatosis and Iron Overload Screening (HEIRS) Study.⁶ We compared characteristics of 312 Cases (high-iron phenotypes, regardless of *HFE* genotype) and 86 Controls [normal iron phenotypes and

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HFE wt/wt (wild type)] using univariate methods. We computed these variables across HOMA-IR quartiles: age; sex; Case/Control; body mass index (BMI); systolic and diastolic blood pressures (SBP and DBP); blood neutrophils and lymphocytes; serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities; elevated C-reactive protein (CRP >0.5 mg/L); transferrin saturation (TS); and serum ferritin (SF). Using backward stepwise and logistic regressions and appropriate independent variables, we determined significant associations of HOMA-IR values, HOMA-IR fourth quartile, and MetS. These results are discussed in the context of previous reports of IR and MetS in African Americans without diabetes.

Materials and Methods

Subjects

The National Institutes of Health HEIRS Study (January 2000 to January 2006) evaluated the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impacts of hemochromatosis and iron overload in a multi-ethnic, primary care-based sample of 101,168 adults enrolled over a 2-year period at 4 Field Centers in the United States and 1 in Canada. This Study was conducted in accordance with the principles of the Declaration of Helsinki. Participants, at least 25 years of age, who gave informed consent, were recruited from a health maintenance organization, diagnostic blood collection centers, and public and private primary care offices in ambulatory clinics associated with the Field Centers.⁷ Self-identified African Americans/non-Hispanic blacks were recruited predominantly from Washington, DC (Howard University), and central Alabama (University of Alabama at Birmingham). Initial screening of HEIRS Study participants included phenotyping (serum iron and unsaturated iron-binding capacity, calculated TS, and SF) and *HFE* genotyping (p.C282Y and p.H63D alleles).⁷

Clinical examination

The study protocol was approved by the institutional review board of each Field Center and informed consent was obtained for CE participation.⁶ Use of HOMA-IR to quantify IR and its relationship to diabetes in HEIRS Study CE participants was approved prospectively by the Study investigators. CE invitations were extended to participants defined as Cases: TS and SF values exceeded study thresholds (TS >50% and SF >300 µg/L for men; TS >45% and SF >200 µg/L for women).⁶ Control participants with TS and SF levels between the 25th and 75th percentile of sex-specific distributions at initial screening without *HFE* p.C282Y or p.H63D alleles (*HFE* wt/wt, by definition) were frequency matched for age and sex to Cases studied at each Field Center and were invited to undergo CE. Participants eligible for CE were informed of their TS, SF, and initial screening genotype. The median interval between initial screening and CE participation was 8 months. The CE included a questionnaire addressing medical history and medications and a focused physical examination to document symptoms and clinical conditions associated with hemochromatosis and iron overload.⁶

At CE, a morning fasting blood sample was obtained to confirm initial screening *HFE* genotype and to perform complete blood count (Beckman Coulter GenS; Beckman/Coulter, Fullerton, CA), measurements of serum ALT and AST activities, serum CRP, serum glucose (Hitachi 9/11 Analyzer; Roche Applied Science, Madison, WI), serum insulin (DPC Immulite Analyzer; Diagnostic Products, Los Angeles, CA), and TS and SF (Hitachi 9/11 Analyzer; Roche Applied Science).^{7,8} Using values of control participants that represented normal ranges of SF, the total coefficient of variation for this device was 5.82%–6.78%. For higher range SF standards, the total coefficient of variation was 5.98%–8.24%.⁹ In participants with elevated ALT activities, reflex testing for hepatitis B surface antigen and hepatitis C antibody was performed (Vitros Eci; Ortho-Clinical Diagnostics Incorporated, Raritan, NJ). All testing was performed at the HEIRS Study Central Laboratory (Fairview-University Medical Center Clinical Laboratory, University of Minnesota, Fairview, MN).

Participant exclusions

The preliminary dataset consisted of observations on 484 self-identified African Americans/non-Hispanic blacks who reported that they did not have diabetes diagnoses (initial screening and CE) and whose medication list at CE did not include antidiabetes drugs. We excluded 71 participants because they fasted <8 h before their CE blood specimens were drawn for measurement of glucose, insulin, and other analytes ($n=9$); had undiagnosed diabetes (serum glucose >126 mg/dL after a fast of ≥ 8 h¹⁰; $n=8$); had serologic positivity diagnostic of hepatitis B or hepatitis C (CE), or a diagnosis of cirrhosis ($n=53$); or were pregnant ($n=1$). We excluded 15 other participants because their datasets were incomplete.

Definition of HOMA-IR

IR was estimated using HOMA-IR [(serum glucose [mg/dL] $\times$ serum insulin [mIU/L])/405].⁴ HOMA-IR values were divided as quartiles, yielding corresponding HOMA-IR ranges. Participants whose HOMA-IR values were in the fourth quartile were defined as having IR.⁴

Definition of MetS

The International Diabetes Federation and other groups define MetS as central obesity and at least two of the following attributes: elevated serum triglycerides; decreased high-density lipoprotein cholesterol (HDL-C); SBP ≥ 130 mmHg or DBP ≥ 85 mmHg; and fasting serum glucose ≥ 100 mg/dL.^{11,12} The HEIRS Study did not measure serum lipid levels. Accordingly, we used a conservative definition for MetS that included these components of the International Diabetes Federation MetS criteria: (1) BMI ≥ 30 kg/m²; (2) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg; and (3) fasting serum glucose ≥ 100 mg/dL.^{11,12} We used BMI as a surrogate of central obesity.^{3,11} We grouped positivity for these attributes into a dichotomous MetS variable.¹³

Statistics

There were complete observations in 398 participants. Distributions of SBP, DBP, and TS values in all participants and in participants grouped by HOMA-IR quartiles were

normal (normal probability plots, d'Agostino's test). We used natural log (ln) transformation to normalize other data (age, BMI, neutrophils, lymphocytes, ALT, AST, and SF). Each mean ln-transformed datum was converted to an anti-ln [95% confidence interval (CI)] for display. Dichotomous variables included the following: sex; Case/Control; *HFE* wt/wt; and CRP >0.5 mg/L.

Descriptive data are displayed as enumerations, percentages, mean $\pm$ 1 standard deviation (SD), or geometric mean (95% CI). Means of normally distributed and normalized data were compared using Student's *t*-test (two tailed). Proportions were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. For some proportions, we computed the 95% CI using continuity correction. We computed the Pearson correlation coefficient and value of *P* for linear regressions of the independent variable HOMA-IR quartiles 1–4 versus the respective dichotomous or continuous variables as a measure of trend. Odds ratios (ORs) and 95% CI are displayed for logistic regressions.

Backward stepwise linear regression on HOMA-IR values was performed to identify significant associations among available independent variables. We performed logistic regression on HOMA-IR fourth quartile (dichotomous) and MetS (dichotomous) using available independent variables.

Analyses were performed with SAS v. 9.1 (SAS Institute Inc., Cary, NC), Excel 2000® (Microsoft Corp., Redmond, WA), and GB-Stat® (v. 10.0; Dynamic Microsystems, Inc., Silver Spring, MD). We defined nominal values of *P* < 0.05 to be significant, but applied Bonferroni corrections to control the type I error rate at 0.05 for multiple univariate comparisons, as appropriate.

Results

General characteristics

Mean age of 398 participants (312 Cases and 86 Controls) was 51.9 years (50.5–53.3; range 25–87). There were 224

men (56.3%) and 174 women (43.7%). Mean BMI was 24.5 kg/m² (24.1–24.9) in men and 23.8 kg/m² (23.3–24.3) in women (*P* = 0.0419). Twelve men (5.4%) and 10 women (5.7%) had BMI >30.0 kg/m² (*P* = 0.8659). Mean SBP and mean DBP were 126 $\pm$ 19 and 75 $\pm$ 9 mmHg, respectively. SBP $\geq$ 130 mmHg was observed in 131 participants (32.9%). DBP $\geq$ 85 mmHg was observed in 64 participants (16.1%).

Mean TS was 47% $\pm$ 14% in men and 39% $\pm$ 13% in women (*P* < 0.0001). Mean SF was 406 μ g/L (375–441; range 47–2,900) in men and 199 μ g/L (174–229; range 14–4,242) in women (*P* < 0.0001). SF at CE was elevated (>300 μ g/L) in 172 men (76.9%). SF at CE was elevated (>200 μ g/L) in 102 women (58.6%). *HFE* wt/wt was detected in 91.0% of participants [204 men (91.1%) and 158 women (90.8%; *P* = 0.9267)]. *HFE* genotypes p.H63D/wt and *HFE* p.H63D/p.H63D were detected in 34 participants [8.5% (95% CI: 0.06–11.8)] and 2 participants [0.1% (95% CI: 0.0009–0.02)], respectively. No participant had *HFE* p.C282Y.

Comparisons of Cases and Controls

Nominal values of *P* are displayed in Table 1. After Bonferroni corrections (significant *P* < 0.0036), the proportions of men, mean ALT, mean AST, mean TS, and mean SF were higher in Cases than Controls. By definition, the proportion of *HFE* wt/wt genotypes was higher in Controls than Cases (Table 1).

First versus fourth HOMA-IR quartiles

Nominal values of *P* are displayed in Table 2. After Bonferroni correction (significant *P* < 0.0036), mean HOMA-IR fourth quartile values of age, BMI, SBP, and ALT were significantly higher than corresponding mean HOMA-IR first quartile values (Table 2).

Trends across HOMA-IR quartiles

Nominal values of *P* are displayed in Table 2. After Bonferroni correction (significant *P* < 0.0036), a

TABLE 1. CHARACTERISTICS OF 398 AFRICAN AMERICANS WITHOUT DIABETES

Characteristics	Cases (n = 312) ^b	Controls (n = 86) ^b	Value of <i>P</i> ^a
Mean age, years (SD)	51.6 (49.9–53.2)	53.0 (50.2–55.9)	0.3883
Men, %	61.9 (193)	36.0 (31)	<0.0001
<i>HFE</i> wt/wt, %	88.5 (276)	100.0 (87)	0.0009
Mean BMI, kg/m ²	24.3 (24.1–24.8)	23.7 (22.9–24.5)	0.1735
Mean SBP, mmHg	126 $\pm$ 18	125 $\pm$ 20	0.5712
Mean DBP, mmHg	75 $\pm$ 10	76 $\pm$ 9	0.1834
Mean neutrophils $\times 10^3/\mu$ L	2.7 (2.6–3.0)	3.0 (2.7–3.4)	0.0842
Mean lymphocytes $\times 10^3/\mu$ L	1.6 (1.6–1.7)	1.5 (1.4–1.7)	0.1149
Mean ALT, IU/L	26 (25–28)	20 (18–23)	0.0001
Mean AST, IU/L	25 (24–26)	21 (21–23)	0.0001
Mean TS, %	46 $\pm$ 14	33 $\pm$ 10	<0.0001
Mean SF, μ g/L	412 (384–437)	83 (80–112)	<0.0001
CRP >0.5 mg/L, % (n)	7.1 (22)	16.3 (14)	0.0083
Mean HOMA-IR	1.67 (1.54–1.81)	1.64 (1.41–1.92)	0.8852

Results are displayed as mean $\pm$ 1 SD, mean (95% CI), or as percentage (n).

^aThese nominal values of *P*. Bonferroni correction for 14 comparisons yielded a revised *P* for significance of <0.0036.

^bCases were defined as participants with any *HFE* genotype whose initial screening TS and SF values exceeded study thresholds (TS >50% and SF >300 μ g/L for men; TS >45% and SF >200 μ g/L for women). Controls were participants who had neither *HFE* C282Y nor H63D (defined as *HFE* wt/wt), and who had TS and SF levels between the 25th and 75th percentiles of sex-specific distributions. *HFE* p.C282Y was not detected in this cohort.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; SD, standard deviation; SF, serum ferritin; TS, transferrin saturation; wt, wild type.

TABLE 2. CHARACTERISTICS OF 398 AFRICAN AMERICANS WITHOUT DIABETES

Characteristics	HOMA-IR quartiles				Value of P (quartile 1 vs. 4) ^a	Value of P (correlation coefficient) for trend ^b
	1 (n=99)	2 (n=100)	3 (n=99)	4 (n=100)		
HOMA-IR, range	≤1.11	1.12–1.66	1.68–2.40	≥2.42	—	—
Mean age, years	48 (45–51)	54 (51–56)	51 (49–54)	55 (52–58)	0.0006	0.2652
Male, % (n)	58.6 (58)	55.0 (55)	55.6 (55)	56.0 (56)	0.7123	0.4145
Cases, % (n) ^c	77.8 (77)	74.0 (74)	80.8 (80)	81.0 (81)	0.4864	0.3542
HFE wt/wt, % (n)	90.9 (90)	90.0 (90)	90.9 (90)	92.0 (92)	0.7831	0.3376
Mean BMI, kg/m ²	22.1 (21.5–22.7)	23.7 (23.2–24.2)	24.8 (24.2–25.4)	26.4 (25.6–27.2)	<0.0001	0.0025
Mean SBP, mmHg	118 ± 16	125 ± 17	128 ± 20	132 ± 19	<0.0001	0.0168
Mean DBP, mmHg	73 ± 9	74 ± 9	76 ± 9	77 ± 10	0.0037	0.0101
Mean neutrophils × 10 ³ /μL	2.9 (2.7–3.1)	2.9 (2.6–3.2)	3.0 (2.7–3.3)	2.4 (2.1–2.8)	0.0304	0.3326
Mean lymphocytes × 10 ³ /μL	1.5 (1.4–1.6)	1.6 (1.5–1.7)	1.7 (1.6–1.8)	1.7 (1.6–1.9)	0.0093	0.0561
Mean ALT, IU/L	21 (18–23)	22 (20–25)	26 (24–29)	31 (28–35)	<0.0001	0.0345
Mean AST, IU/L	24 (22–25)	23 (21–24)	24 (22–25)	27 (25–29)	0.0254	0.2546
Mean TS, %	47 ± 15	43 ± 15	42 ± 13	42 ± 14	0.0294	0.1323
Mean SF, μg/L	272 (229–322)	261 (219–311)	302 (257–354)	365 (300–433)	0.0153	0.1148
CRP >0.5 mg/L, % (n)	5.1 (5)	5.0 (5)	9.1 (9)	17.0 (17)	0.0072	0.0879

HFE wt/wt was defined as HFE genotypes without allele p.C282Y or p.H63D. Results are displayed as range, mean ± 1 SD, mean (95% CI), or percentage (n).

^aThese nominal values of *P*. Bonferroni correction for 15 comparisons yielded a revised *P* for significance of <0.0036.

^bThese nominal values represent *P* (Pearson correlation coefficient) for linear regressions of the respective dichotomous or continuous variables by the independent variable HOMA-IR quartile 1–4. Bonferroni correction for 15 comparisons yielded a revised *P* for significance of <0.0033.

^cCases were defined as participants whose initial screening TS and SF values exceeded study thresholds without regard to HFE genotype. Controls were participants who had neither HFE C282Y nor H63D (defined as HFE wt/wt), and who had TS and SF levels between the 25th and 75th percentiles of sex-specific distributions. HFE p.C282Y was not detected in this cohort.

significant increasing trend was observed in mean BMI only (Table 2).

Regression on HOMA-IR values

Backward stepwise regression on HOMA-IR values revealed these positive associations: age (*P*=0.0026); BMI (*P*<0.0001); lymphocytes (*P*=0.0125); SF (*P*=0.0388); and CRP >0.5 mg/L (*P*<0.0001). We identified these negative associations: neutrophils (*P*=0.0460) and TS (*P*=0.0010). This model accounted for 22.9% of the variance in HOMA-IR values [analysis of variance (ANOVA) *P*<0.0001].

Regression on HOMA-IR fourth quartile

Logistic regression on HOMA-IR fourth quartile (dichotomous) revealed these positive associations: age [*P*=0.0006; OR 1.0 (1.0–1.1)]; BMI [*P*<0.0001; OR 1.3 (1.2–1.4)]; ALT [*P*=0.0068; OR 1.0 (1.0–1.1)]; SF [*P*=0.0040; OR 1.0 (1.0–1.1)]; and CRP >0.5 mg/L [*P*=0.0193; OR 2.7 (1.2–6.3)]. There was one negative association: TS [*P*=0.0037; OR 0.97 (0.95–0.99)]. This model accounted for 20.7% of the variance in HOMA-IR fourth quartile (ANOVA *P*<0.0001). Because an OR of 1.0 (or close to 1.0) indicates that the odds of exposure among case participants are the same as, or similar to, the odds of exposure among controls¹⁴, the ORs of practical importance identified by this regression are BMI and CRP >0.5 mg/L.

Metabolic syndrome

Fourteen participants (3.5%; 7 men, 7 women) had MetS. Ten of 14 participants with MetS (71.4%) also had IR.

Logistic regression on MetS revealed one positive association: IR [*P*=0.0010; OR 7.4 (2.1–25.2)]. This model accounted for 14.0% of the variance in MetS (ANOVA *P*<0.0041).

SF in IR and MetS

Mean SF was significantly greater in participants with IR than without IR. Mean SF did not differ significantly in participants with and without MetS (Table 3).

Discussion

HOMA-IR values were significantly associated with age, BMI, lymphocytes, SF, and CRP >0.5 mg/L in these 398 African American HEIRS Study participants without diabetes, although the association of HOMA-IR values with

TABLE 3. SERUM FERRITIN, INSULIN RESISTANCE, AND METABOLIC SYNDROME IN 398 AFRICAN AMERICANS

Characteristics	No. of subjects	Mean SF, μg/L (95% CI)	Value of P
Insulin resistance	100	365 (308–433)	
No insulin resistance	298	278 (252–306)	0.0061
Metabolic syndrome	14	286 (167–490)	
No metabolic syndrome	384	298 (273–324)	0.8849

Insulin resistance was defined as HOMA-IR fourth quartile. Metabolic syndrome was defined as concurrence of these three attributes: BMI ≥30 kg/m²; SBP ≥130 mmHg or DBP ≥85 mmHg; and fasting serum glucose ≥100 mg/dL.

SF in regression analyses was weak ($P=0.04$). There were significant negative associations of HOMA-IR values with neutrophils and TS. HOMA-IR quartiles were associated with significant increments of BMI alone. In 5,959 NHANES (1988–1994) participants without diabetes, HOMA-IR values were higher in African Americans than whites and higher in older than younger participants.² SF values 1 SD above the corresponding means were also associated with significantly higher HOMA-IR values, after adjustment for other factors.² “Clinically elevated” CRP levels (>1.0 mg/L) were associated with 63% higher HOMA-IR values.²

IR defined as HOMA-IR fourth quartile (≥ 2.42) was significantly associated with BMI in these participants, after adjustment for other variables. In adult participants without diabetes in the NHANES Study (1988–1994), mean fasting insulin levels were higher in univariate analyses in black women than white women at all BMI levels ≤ 30 kg/m².¹⁵ In Dallas Heart Study participants without diabetes, the mean value of HOMA-IR was significantly greater in African American women than Caucasian women.¹⁶ Insulin sensitivity was significantly lower in African American women than Caucasian/white women in four studies,^{17–20} and significantly lower in South African black women than South African white women in another report.²¹ In adults of similar BMI, IR was more common in African Americans than non-Hispanic whites.¹⁸

IR defined as HOMA-IR fourth quartile was also significantly associated with CRP >0.5 mg/L in this study, after adjustment for other variables. In the multicenter population-based Insulin Resistance Atherosclerosis Study, CRP levels were inversely and independently associated with insulin sensitivity in blacks and non-Hispanic whites without diabetes.²² In a study of healthy, overweight, premenopausal women without diabetes, CRP alone was independently associated with insulin sensitivity.²⁰ In the same cohort, insulin sensitivity was significantly lower in African American women than white women, after adjusting for CRP and other markers of obesity and inflammation.²⁰

MetS occurred in 3.6% of these African Americans without diabetes. After adjustment for other variables, MetS was significantly associated with IR alone. In contrast, the age-adjusted prevalence of MetS in African Americans unselected for diabetes diagnoses in NHANES (1988–1994) was 21.6%.²³ The prevalence of MetS was 57% higher in African American women than African American men,²³ a difference attributed to the higher prevalence of type 2 diabetes, elevated BP, and obesity/physical inactivity in African American women than African American men.²⁴ In this cohort, exclusion of participants with diabetes, the predominance of men, and our conservative definition of MetS that did not include triglyceride and HDL-C criteria could account, in part, for the relatively low prevalence of MetS that we observed.²³

Mean SF was significantly higher in these participants with IR than in participants without IR, but the OR of the association of SF with IR in multivariable regressions was only 1.0. In another study, mean SF in 769 non-Hispanic white HEIRS Study participants without diabetes with and without IR did not differ significantly.¹³ In 6,044 adult NHANES (1988–1994) participants without elevated serum iron/SF measures, there were positive associations of SF with IR and MetS, but mean SF (95% CI) in all subgroups²⁵ were not elevated based on this sex-specific study thresholds for SF.

Case/Control status in this study was not significantly associated with HOMA-IR values, IR, or MetS. These Cases included no participant with *HFE* p.C282Y homozygosity or p.C282Y/p.H63D compound heterozygosity, the predominant *HFE* genotypes associated with increased risk to develop iron overload in adults who reside in North America.⁸ Hemochromatosis-associated *HFE* genotypes are rare in African Americans/non-Hispanic blacks.²⁶

Prevalence and incidence rates of hepatitis B and hepatitis C are higher in African Americans than in other American race/ethnicity groups.^{27–29} Both hepatitis B and hepatitis C are significantly associated with IR.^{30,31} In a review,³² many but not all studies reported that the risk of MetS is lower in patients with hepatitis B than in control subjects, especially men, and that the risk of diabetes is probably not increased in patients with chronic hepatitis B.³² Analyses of NHANES (1988–1994) data revealed that hepatitis C was not associated with MetS, after adjustment for other variables.³³ In this study, we excluded 53 of 484 (11.0%) of preliminary subjects because they had serologic positivity diagnostic of hepatitis B or hepatitis C, or a diagnosis of cirrhosis. Based on the conclusions of other studies,^{30,31} it is plausible but unproven that mean HOMA-IR would have been higher in these excluded subjects than in the 398 subjects whose observations we analyzed. Having included subjects with serologic positivity diagnostic of hepatitis B or hepatitis C is unlikely to have increased proportions of subjects with MetS, based on previous reports.³²

These regression analyses indicate that variables other than those we studied are also significantly associated with the pathogenesis or occurrence of IR and MetS in African Americans. For example, a transethnic meta-analysis of genetic determinants of fasting glucose and insulin levels in persons of African ancestry without diabetes revealed single-nucleotide polymorphisms (SNPs) of statistical significance that were shared and unshared with European Americans.³⁴ A genome-wide association study of BMI detected an allele in the semaphorin-4d gene (*SEMA4D*; rs80068415; “C” allele frequency 0.008) in African Americans and West Africans, but not in Europeans or Asians.³⁵ Higher levels of semaphorin-4d were significantly associated with obesity and *SEMA4D* CT (vs. TT) genotypes.³⁵ A genome-wide association study of African Americans and West Africans without diabetes revealed novel SNPs associated with fasting insulin levels and IR, in addition to other SNPs associated with IR and type 2 diabetes in whites.³⁶ Serum adiponectin is positively correlated with serum insulin.³⁷ Mean serum adiponectin levels are significantly lower in African Americans than whites.^{37,38} In African Americans with normal glucose tolerance, mean plasma adiponectin levels were twofold greater in those with insulin sensitivity than in those with IR.³⁹

Strengths of this study are that this cohort size provides statistical power to estimate independent joint effects in a multivariable model and the study design and results are consistent with observations in a related study of non-Hispanic whites who also attended an HEIRS Study post-screening CE.¹³ Iron phenotypes of Cases and Controls as defined in the HEIRS Study may have affected some statistical outcomes, especially those regarding TS and SF. Case participants had elevated SF levels and Control participants had SF levels between the 25th and 75th percentile of sex-specific distributions at initial screening, according to

the HEIRS Study design.⁶ It is unknown whether using a definition of MetS that included triglycerides and HDL-C levels would have yielded a significant difference between the mean SF of participants with and without MetS. A limitation of the cross-sectional HEIRS Study is that it does not provide longitudinal observations of the proportions and characteristics of participants who will eventually develop progression of metabolic disease, including diabetes and its complications. Accepted measures of body iron stores⁴⁰ were not available for these analyses. Measurement of diverse markers of inflammation, coagulation/thrombotic diathesis, and cardiovascular disease was beyond the scope of the HEIRS Study.

Conclusions

We conclude that IR was associated with BMI and CRP >0.5 mg/L in African Americans without diabetes, after adjustment for other variables. MetS was associated with IR alone.

Acknowledgments

The HEIRS Study (January 2000 to January 2006) was supported by the National Heart, Lung, and Blood Institute, in conjunction with the National Human Genome Research Institute. Individual investigators, grants, and contracts have been acknowledged in detail previously.^{7,8} The authors also acknowledge the HEIRS Study participants and partial support of this work by Southern Iron Disorders Center.

Authors' Contributions

Ja.C.B.: conceived the study, evaluated patients, performed statistics, and drafted the article. J.C.I.B.: performed statistics and drafted the article. R.T.A.: conceived the study, performed statistics, and drafted the article. All authors approved the article in its final form.

Author Disclosure Statement

The authors declare that they have no conflict of interests regarding publication of this work.

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