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Relationships Among Obesity, Inflammation, and Insulin Resistance in African Americans and West Africans

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Abstract

Several research studies in different populations indicate that inflammation may be the link between obesity and insulin resistance (IR). However, this relationship has not been adequately explored among African Americans, an ethnic group with disproportionately high rates of obesity and IR. In this study, we conducted a comparative study of the relationship among adiposity, inflammation, and IR in African Americans and West Africans, the ancestral source population for African Americans. The associations between obesity markers (BMI and waist-to-hip ratio (WHR)), inflammatory markers (high-sensitivity C-reactive protein (hsCRP), haptoglobin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α), and IR (homeostasis model assessment of insulin resistance (HOMAIR)) were evaluated in 247 West Africans and 315 African Americans. In average, African Americans were heavier than the West Africans (by an average of 1.6 BMI units for women and 3 BMI units for men). Plasma hsCRP, haptoglobin, and IL-6 (but not TNF-α level) were higher in African Americans than in West Africans. In both populations, BMI was associated with markers of inflammation and with HOMAIR, and these associations remained significant after adjusting for sex and age. However, the pattern of associations between measured inflammatory markers and IR was different between the two groups. In West Africans, hsCRP was the only inflammatory marker associated with IR. In contrast, hsCRP, haptoglobin, and IL-6 were all associated with IR in African Americans. Interestingly, none of the associations between markers of inflammation and IR remained significant after adjusting for BMI. This finding suggests that in African Americans, the relationship between inflammatory markers and IR is mediated by adiposity.

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Introduction

The prevalence of obesity and overweight is steadily increasing in most human populations and has reached epidemic proportions in many westernized societies. According to the World Health Organization's 2005 global estimates, about 1.6 billion adults are overweight and 400 million are obese (1). Globally, obesity is a major contributor to the burden of disabilities and several chronic diseases including hypertension, type 2 diabetes (T2D), and heart diseases (2,3). In United States, >60% of the adult population is either obese or overweight (3). About 300,000 excess deaths are linked to obesity and its complications annually, making obesity the second leading cause of premature death in the United States.

Until very recently, adipose tissue was viewed as a relatively inert tissue involved only in the storage of energy in the form of triglycerides. Recent advances in biotechnology and molecular techniques have provided contrary evidence, especially for white adipose tissue. It is now well known that adipose tissues are active endocrine tissues that produce >50 proteins (known as adipokines), including leptin, adiponectin, resistin, interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β, vascular endothelial growth factor, nerve growth factor, and haptoglobin (4). Moreover, it is now clear that adipose tissues participate in the regulation of several physiologic and pathologic pathways such as metabolism, immunity, and inflammation (5).

Following the observation that serum concentrations of a number of inflammatory markers including CRP, TNF-α, obesity is now viewed as a low-grade inflammatory disease (5–8). Physiologically, obesity may also be viewed as a state of metabolic dysfunction (or metabolic disease) in which insulin function is frequently impaired (6, 7, 9, 10). The relationship among obesity, inflammatory markers (such as adipokines, phase reactant proteins), and insulin resistance (IR) has been investigated extensively in several populations (7,9, 11–19) but not explicitly in populations of African descents in which the prevalence of obesity and associated comorbidities is one of the highest in the world. In this study, we evaluated the phenotypic relationship among obesity, inflammatory markers, and IR among African Americans and West Africans.

Methods and Procedures

The 562 unrelated individuals included in this study were selected from two large ongoing genetic epidemiology studies in Washington, DC and in West Africa (Nigeria and Ghana). Each study was approved by the institutional review board at Howard University and at each participating West African university. The West African individuals included in this study were recruited as part of an international collaboration of the US and West African scientists to study the epidemiology and genetics of T2D. A detailed description of the parent study, the Africa America Diabetes Mellitus study has been published elsewhere (10). Briefly, The Africa America Diabetes Mellitus study enrolled and examined T2D cases and controls in three urban centers in Nigeria (Lagos, Ibadan, and Enugu) and two urban centers in Ghana (Accra and Kumasi). The 247 West Africans included in this analysis were selected from the control cohort of the Africa America Diabetes Mellitus study. All subjects were unrelated

and nondiabetic. The African-American sample was drawn from the Howard University Family Study, a population based genetic epidemiology study in the Washington, DC area. The Howard University Family Study sample was not ascertained based on any phenotype. The subjects from the Howard University Family Study included in this study were unrelated and nondiabetic.

To be included in this study, participants were required to be between the ages of 35 and 60 years and not to have diabetes. To ensure that the entire distribution of BMI would be represented in this study, we did not impose any restriction on BMI. Anthropometric measurements (height, weight, waist and hip circumference) were measured in the United States and West Africa using the same standardized protocol. Briefly, weight was measured in light clothes on an electronic scale to the nearest 0.1 kg, and height was measured with a stadiometer to the nearest 0.1 cm. BMI was calculated as weight in kilogram divided by height in meters square (kg/m2). Waist circumference was measured to the nearest 0.1 cm at the narrowest part of the torso as seen from the anterior aspect. All measurements were taken by well-trained clinic staff after each participant completes the informed consent process.

An overnight fasting blood samples were obtained from all participants for the assessment of multiple metabolic traits including glucose, insulin, C-peptide, and other biochemical parameters. All laboratory assays were done in the same laboratory. Plasma TNF-α and IL-6 levels were measured using an enzyme-linked immunosorbent assay (Quantikine HS; R&D Systems, Minneapolis, MN). Serum high-sensitivity C-reactive protein (hsCRP), haptoglobin, and glucose were determined enzymatically with Cobas Integra Plus Analyzer (Roche Diagnostics, Indianapolis, IN). Insulin was measured on an Elecsys1010 immunoassay analyzer (Roche Diagnostics) using an electrochemiluminescence technique. IR was assessed using the scores of homeostasis model assessment of insulin resistance (HOMAIR) calculated as (fasting serum insulin (mU/l) × fasting plasma glucose (mmol/l))/ 22.5 (ref. 20).

All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Data with non-Normal or skewed distributions were logarithmically transformed before analysis to avoid violating the normality assumption of employed statistical algorithms. Continuous variables were expressed as mean ± s.d. and comparisons of group means were performed using Student’s t-tests at a statistical significance level of 0.05. Pearson correlation coefficients (r) were calculated to determine the association between obesity markers, inflammation, and IR. Linear regression analyses were used to determine the predictors of HOMAIR using the obesity markers and/or the inflammatory markers as explanatory variables.

Results

Anthropometric and biochemical profiles of participants included in this study are displayed in Table 1. Overall, the West African participants were significantly leaner than the African Americans for both men and women. The mean BMI for the West African women is 29.0 ± 6.3 kg/m2 compared to 30.6 ± 8.9 kg/m2 for African-American women. The difference in

mean BMI is much higher for the men (West Africans = 25.9 ± 6.3; African Americans = 29.0 ± 7.64 kg/m2). With the exception of TNF-α, plasma levels of inflammatory markers including haptoglobin and hsCRP were lower in West Africans than African Americans (haptoglobin: 107.54 ±61.18 mg/dl vs. 146.42 ± 67.98 mg/dl; hsCRP: 0.49 ± 1.17 mg/dl vs. 0.68 ± 1.24 mg/dl). In contrast, there was no significant difference between the two populations in plasma level of IL-6. Circulating TNF-α was higher in West Africans than African Americans (5.17 ± 4.27 pg/ml vs. 2.11 ± 3.46 pg/ml). BMI and waist-to-hip ratio (WHR) were positively correlated with HOMAIR in both populations. These correlation coefficients were slightly stronger in African Americans than in West Africans. The BMI: HOMAIR correlation coefficient, r, was 0.51 ($P < 0.0001$) among African Americans vs. 0.30 ($P < 0.0001$) among West Africans, and the WHR: HOMAIR r was 0.36 ($P < 0.0001$) among African Americans vs. 0.25 ($P = 0.0007$) among West Africans.

Relationship among inflammatory markers, obesity, and HOMAIR

The set of partial correlation coefficients for inflammatory markers, obesity markers, and IR is shown in Table 2. hsCRP was positively associated with BMI and WHR in both populations. Haptoglobin correlated with WHR but not BMI in both populations. Unexpectedly, TNF-α was negatively associated with BMI in the West African cohort. None of the inflammatory markers was associated with HOMAIR in West Africans, whereas IL-6, hsCRP, and haptoglobin were positively associated with HOMAIR in African Americans. IL-6 was also associated with BMI and WHR in African Americans.

Relationship between obesity markers and HOMAIR using linear regression models

The degree to which obesity markers independently predicted HOMAIR was examined in a series of multiple regression models in both populations. In these models, HOMAIR was the dependent variable and obesity markers the independent variables. BMI (overall degree of heaviness) and WHR (abdominal obesity) were predictors of HOMAIR and this relationship was independent of age and gender in both populations ($\beta_{BMI} = 0.03 \pm 0.01$, $P = 0.002$ and $\beta_{WHR} = 4.09 \pm 1.04$, $P = 0.0001$ in West African vs. $\beta BMI = 0.06 \pm 0.005$, $P < 0.0001$ and $\beta_{WHR} = 4.91 \pm 0.77$, $P < 0.0001$ in African Americans). Furthermore, when BMI and WHR are included together as independent variables, each remained a significant independent predictor of HOMAIR in both populations ($\beta_{BMI} = 0.024 \pm 0.01$, $P = 0.02$ and $\beta_{WHR} = 3.46 \pm 1.07$, $P = 0.0015$ in West Africans vs. $\beta_{BMI} = 0.052 \pm 0.006$, $P < 0.0001$ and $\beta_{WHR} = 2.12 \pm 0.76$, $P = 0.0055$ in African Americans). Thus, overall adiposity (as estimated by BMI) and abdominal adiposity (as estimated by WHR) were independent predictors of IR.

Relationship between inflammatory markers and HOMAIR

To identify the inflammatory markers that would predict HOMAIR, we evaluated a series of linear regression models in which each inflammatory marker was included as independent variable and HOMAIR the dependent variable; all models were adjusted for age and gender. The results of the regression analysis are displayed in Table 3 and Figure 1. As depicted in Figure 1D, only hsCRP is a predictor of HOMAIR ($\beta = 0.13 \pm 0.05$, $P = 0.008$) in West Africans; the association remained after adjusting for age, gender, and BMI or WHR. In African Americans (Figure 1C,E,G), IL-6 ($\beta = 0.17 \pm 0.06$, $P = 0.007$), hsCRP ($\beta = 0.17 \pm 0.04$, $P < 0.0001$), and haptoglobin ($\beta = 0.19 \pm 0.07$, $P = 0.009$) were independent predictors

of HOMAIR. However, when additional adjustments were made including WHR or BMI, a differential association was observed in the African-American cohort; hsCRP and haptoglobin remained predictors of HOMAIR under the model adjusting for WHR (β_{hsCRP} = 0.14 ± 0.0002 and $\beta_{haptoglobin}$= 0.18 ± 0.007, P = 0.005) while they were no longer associated with HOMAIR in the model adjusting for BMI (βhsCRP = 0.03 ± 0.04, P = 0.46 and βhaptoglobin = 0.09 ± 0.06, P = 0.18). Also, the relationship between IL-6 and HOMAIR did not remain significant after adjustment for BMI or WHR (βIL-6/BMI = −0.004 ± 0.06, P = 0.94 and $\beta_{IL\text{-}6/WHR}$ = 0.08 ± 0.06, P = 0.16).

Discussion

We evaluated the relationship between obesity markers (BMI, WHR), inflammation markers (IL-6, TNF-α, haptoglobin, and hsCRP), and IR in populations of African descent. To the best of our knowledge, this study is the first to compare the associations among obesity, inflammation, and IR in African Americans and West Africans. The individuals included in this study were selected from a pool of those with low prevalence of cardiovascular diseases and other inflammatory diseases to minimize the odds of reverse causation. Also, each study sample included a wide range of measures of adiposity and IR.

Results from this study confirmed previously reported associations between markers of obesity (BMI and WHR) and IR measured by HOMA (21–23). In both populations, all measures of adiposity were positively correlated with HOMAIR. Observed associations were, however, stronger in African Americans than in West Africans (31% of HOMAIR variation can be explained by BMI and WHR in African Americans compared to 11% in West Africans). This difference can be explained, in part, by the difference in overall obesity between the two populations; on average, African Americans were heavier than the West Africans. In all, we demonstrated that both BMI and WHR are independent predictors of IR in these populations of African ancestry.

Previous studies have shown that obesity, especially abdominal obesity, is associated with low-grade inflammation, which is characterized by an increase in plasma concentration of inflammatory markers such as hsCRP, haptoglobin, TNF-α, IL-6, and other cytokines and chemokines (24,25). Consistent with previous findings (17, 26–31), we observed significant association among hsCRP, haptoglobin, and BMI in both West Africans and African Americans. The associations between WHR and markers of inflammation were different between the West Africans and African Americans. For example, only hsCRP was associated with WHR in West Africans. The association between WHR and hsCRP has been shown to be a risk factor not only for the development of obesity-related IR but also for cardiovascular diseases in different populations (31, 32). This observation may help explain the coexistence of metabolism syndrome and cardiovascular diseases in obese and T2D patients. In contrast to previous reports (9, 33, 34), we did not observe significant association among TNF-α, obesity, and inflammatory markers in the two populations studied. Given that TNF-α is one of the key cytokines that is produced as the mass of white adipose tissue increases and has been linked to IR in cellular and animal models (35–37), the lack of association in this study is therefore striking. It is important to confirm these results in similar studies with larger sample size. In this regard, the role of TNF-α in the

pathophysiology of IR in this study has to be interpreted with caution. IL-6, another important adipokines and marker of inflammation, showed association with obesity markers and IR only in African Americans even though there was no significant difference between the two populations in the plasma level of circulating IL-6. As suggested above, it is also possible that the difference in sample size between the two populations could be partly responsible for the absence of expected associations in West Africans.

The degree to which HOMAIR may be predicted by markers of inflammation was assessed in different univariate and multivariate regression models. In West Africans, hsCRP was a significant predictor of HOMAIR in a model that included age and sex. However, only 5% of HOMAIR variation as measured by R2 was explained by hsCRP. Interestingly, the addition of BMI or WHR resulted in moderate increase in observed R2, respectively, to 8 and 11% for BMI or WHR. Taken together, the model that included both WHR and hsCRP provided better explanation for observed variability in HOMAIR than hsCRP alone or hsCRP and BMI together. Following the above observation, it is reasonable to suggest that the relationship between IR and hsCRP is to a significant extent dependent on adiposity especially abdominal adiposity. Similar to the results in West Africans, hsCRP and WHR (r2 = 16%) predicted HOMAIR better than hsCRP alone (r2 = 7%) in African Americans; in the same fashion haptoglobin was also a predictor of HOMAIR. These findings provide support for the important role of abdominal adiposity in the development of IR as previously reported. The association between IL-6 and IR did not remain significant after adjusting for BMI or WHR suggesting that observed relationship is indirect and heavily influenced by obesity. The observation suggests that a significant proportion of the relationship between IR and inflammatory markers in African Americans is mediated by differences in the distribution of adiposity parameters.

This study has several strengths. First, it provides much needed data in two populations of African descent with contrasting levels of obesity. Second, several markers were measured for obesity and inflammation, thereby providing a finer grained understanding of the relationships between these markers and IR. On the other hand, the sample sizes are modest and larger samples will be needed to generalize these findings. In addition, it should be noted that the West African subjects had higher BMI than the general population in their communities. This is because they comprised family members of subjects with T2D and were enrolled from urban areas, both of which are associated with higher levels of obesity in West Africa. Therefore, the findings among the West Africans may not be representative of the general population. Nonetheless, the data obtained would prove useful figures for comparison in future studies.

In summary, the major findings observed in this study conducted in populations of African ancestry are consistent with previous observations in other global ancestry populations as follows: (i) obesity is directly associated with IR; (ii) obesity is associated with inflammation especially to hsCRP, haptoglobin, and IL-6; (iii) the association between inflammation and IR is for the most part driven by adiposity and appears to be stronger in African Americans than in West Africans; and (iv) overall adiposity, as measured by BMI, may not be the best marker in accessing the relationship between IR and inflammation in the obese state, especially in African Americans. This study did not provide evidence for

reported association between some key cytokines such as TNF-α in the association among obesity, inflammation, and IR. Further studies are needed to confirm, explain, and extend the findings of similarities and differences seen between African Americans and West Africans in this study, especially in light of differences in diet, physical activity, lifestyles, and other environmental factors between the two populations. Such findings could potentially contribute to our understanding, management, and treatment of obesity-related diseases in multiple human populations.

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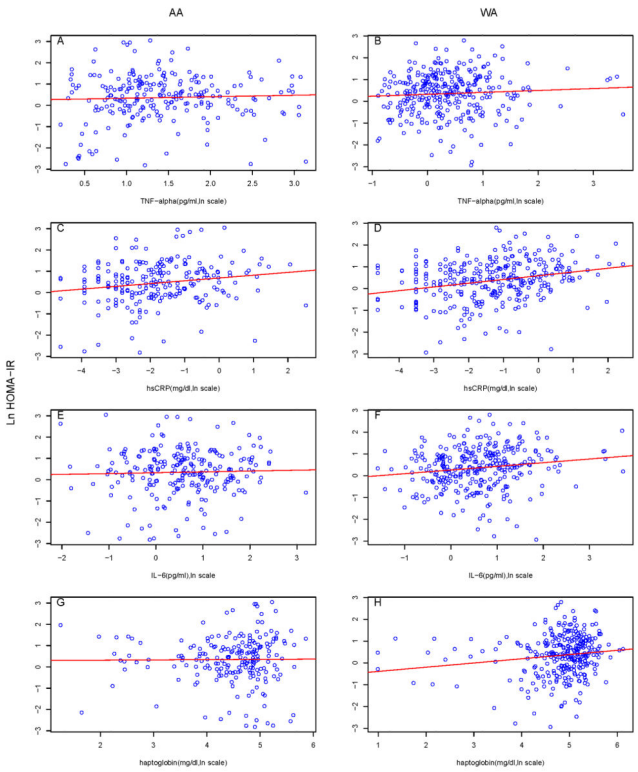

Figure 1.

Univariate relationship of HOMAIR with (**A, B**) TNF-α, (**C, D**) hsCRP, (**E, F**) IL-6, and (**G, H**) haptoglobin in AA (left panel) and WA (right panel).

AA, African Americans; HOMAIR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; WA, West Africans.

Table 1

Anthropometric and biochemical profiles of study populations by gender

	West Africans		African Americans	
	Male (n=84)	**Female (n=163)**	**Male (n=148)**	**Female (n=167)**
Age (years)	49.62±7.77 50.1 (34.6, 63.6)	**46.19±7.29**** 45.6 (32, 61)	46.5±6.52 45.5 (35,61)	46.18±6.9 46.0 (35,63)
BMI(Kg/m^2)	25.9±6.31 25.3 (15.9,60.2)	**29.03±6.33**** 28.0(17.3,51.6)	29.04±7.65 28.6 (18,59.1)	30.64±8.98 29.2(17.1,56.1)
WHR	0.89±0.07 0.89 (0.75, 1.1)	**0.86±0.07*** 0.86 (0.67,1.2)	0.91±0.06) 0.91 (0.79,1.1)	**0.85±0.07**** 0.85 (0.63,1.1)
Hapt. (mg/dL)	93.29±58.3 88.3 (3.5, 279.9)	**114.61±61.43*** 115.9 (9.6,348.2)	135.99±66.61 134.1 (2.7,418.7)	**155.7±68.04*** 151.6 (2.70,451.9)
hsCRP (mg/dL)	0.42±0.83 0.16 (0.01, 5.9)	0.54±1.31 0.15 (0.01, 12.4)	0.54±1.28 0.22 (0.01,11.4)	0.81±1.2 0.33 (0.01,7.7)
IL-6 (pg/mL)	2.53±2.34 1.79 (0.13, 11.1)	2.68±2.78 1.78 (0.16,24.4)	2.59±4.27 1.66 (0.21,40.9)	3.05±4.63 1.85 (0.24,41.7)
TNF-α (pg/mL)	5.26±4.67 3.33 (1.24,21.6)	5.13±4.07 3.75 (1.32,23.0)	1.66±1.43 1.24 (0.41,11.1)	**2.5±4.53*** 1.44 (0.41,34.4)
HOMA-IR	1.93±2.41 1.32 (0.08,14.3)	2.62±3.3 1.62 (0.06,21.0)	2.09±2.25 1.54 (0.06,16.2)	2.15±2 1.53 (0.05,14.2)

Data are expressed as mean ± SD (Upper values) and median/interquartile range (lower values). M, male; F, female; WHR: Waist-to-hip ratio; Hapt: haptoglobin; hsCRP: high sensitive C-reactive protein, IL-6: interleukin-6

* P<0.01,

** P<0.001;

P values are for mean test comparing gender within group. P values < 0.05 are indicated in bold

Table 2

Sex-adjusted correlation coefficients for markers of inflammatory, obesity, and HOMA-IR

	Correlation coefficients (r)							
	West Africans				African Americans			
Variables	**Ln IL-6**	**Ln TNF-α**	**Ln hsCRP**	**Ln haptoglobin**	**Ln IL-6**	**Ln TNF-α**	**Ln hsCRP**	**Ln haptoglobin**
BMI	−0.05	**−0.21****	**0.35****	**0.20****	**0.29****	0.06	**0.45****	**0.13***
WHR	−0.02	0.006	**0.22****	0.13	**0.19****	0.10	**0.18***	−0.008
Ln HOMA-IR	−0.03	−0.003	0.12	0.007	**0.17****	0.06	**0.28****	**0.13****

Ln, logarithm; IL-6, interleukin-6; TNF-α, tumor necrosis factor- alpha; hs CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment insulin resistance

*P<0.01,

**P<0.001;

BMI, body mass index; WHR, waist-to-hip ratio. P values <0.05 are indicated in boldface.

Table 3

Association between ln HOMA-IR and inflammatory markers from linear regression in West Africans and African Americans

Dependent variable: HOMA-IR							
		Univariate Model			Adjusted Model (age, gender)		
Population	**Inflammatory markers**	**β**	**SE (β)**	**p**	**β**	**SE (β)**	**p**
West Africans	IL-6	0.04	0.08	0.62	0.02	0.08	0.77
	TNF-α	0.07	0.11	0.52	0.06	0.11	0.58
	hsCRP	0.13	0.05	**0.008**	0.13	0.05	**0.008**
	Haptoglobin	0.01	0.1	0.9	-0.04	0.1	0.71
African Americans	IL-6	0.17	0.06	**0.007**	0.15	0.06	**0.01**
	TNF-α	0.09	0.08	0.25	0.08	0.08	0.32
	hsCRP	0.17	0.04	**<.0001**	0.17	0.04	**<.0001**
	Haptoglobin	0.19	0.07	**0.009**	0.18	0.07	**0.02**

β: regression coefficient; $HOMA_{IR,}$ homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

P values < 0.05 are indicated in boldface.

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