Inflammatory Biomarkers in African Americans: A Potential Link to Accelerated Atherosclerosis

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Experimental evidence demonstrates that inflammation plays a key role in the pathogenesis of an atherosclerotic plaque. Whereas multiple, large, prospective epidemiologic studies demonstrate that C-reactive protein (CRP) and other inflammatory biomarkers predict future risk of cardiovascular disease (CVD), data on inflammation among specific ethnic groups in the United States are sparse. For example, CRP levels may vary by race/ethnicity but more data are needed to better assess this issue. Additionally, data on the relationship between white blood cell (WBC) count and CVD among African American and Hispanic participants suggest that elevated WBC is associated with increased likelihood of vascular disease. Furthermore, some research suggests that African Americans may have different fibrinolytic characteristics than white Americans. Generally, fibrinogen levels have been noted to be higher among African Americans than among white Americans. Although data regarding inflammatory biomarkers of CVD in various ethnic groups are slowly emerging, the lack of adequate representation of African Americans in clinical cohorts continues to be the limiting factor in data ascertainment.

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Although traditional risk factors for cardiovascular disease (CVD), such as hypertension, diabetes, smoking, and hypercholesterolemia have been identified as important mediators of CVD development and progression, 20% of all incident cardiovascular events occur among individuals with no traditional risk factors.[1] Due to scientific focus on the basic model of atherosclerosis,

Table 1
Inflammatory Biomarkers With Possible Predictive Value in Cardiovascular Disease

- C-reactive protein
- Interleukin-6
- Intercellular adhesion molecule
- White blood cell count
- Fibrinogen
- Serum amyloid A

viewing low-density lipoprotein (LDL) and foam cell levels as principal mediators of plaque formation, the reduction of elevated cholesterol levels has been an important component of CVD risk attenuation. Additionally, experimental evidence demonstrates that inflammation plays a key role in atherosclerotic plaque formation and rupture,[2] and that statins, which have traditionally been used to lower cholesterol levels, also have anti-inflammatory effects.[3]

To date, several markers of inflammation have been evaluated as predictors of cardiovascular disease (Table 1). Of these markers, the most extensive and consistent data have been associated with C-reactive protein (CRP). However, although multiple large, prospective epidemiologic studies demonstrate that CRP predicts future risk of CVD,[4,5] data on inflammation among specific ethnic groups in the United States are sparse.

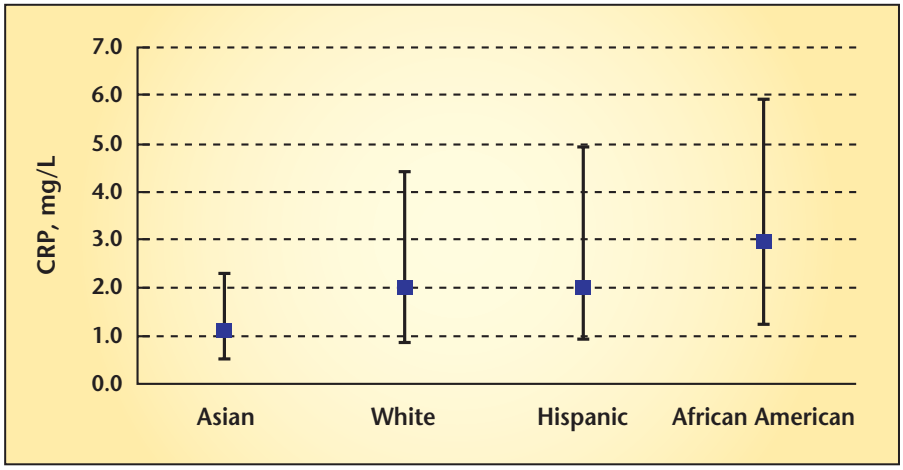
Distribution of CRP Levels by Race/Ethnicity

Data from the National Health and Nutrition Examination Survey (NHANES) and our group indicate certain racial/ethnic differences in CRP levels among U.S. women. Ford and associates[6] utilized data from the NHANES 1999-2000 data set and found that age-adjusted, geometric, mean levels of CRP among white women (N = 963; CRP = 2.3 mg/L) were lower than the CRP levels of either African American (N = 419; CRP = 3.1 mg/L, $P < .007$) or Mexican American women (N = 618, CRP = 3.5 mg/L, $P < .001$). After excluding women taking hormone replacement therapy (HRT) and those with CRP levels > 10 mg/L, this relationship among racial/ethnic groups persisted. However, the difference noted in CRP levels between white and African American women was not statistically significant after adjustment for potential confounders. Triglyceride levels, waist circumference, and systolic blood pressure were important determinants of CRP levels in this cohort. The authors hypothesized that the higher CRP levels among Mexican American women might suggest that they are at higher risk for CVD.

Likewise, utilizing data from the Women's Health Study cohort, our group assessed the distribution of CRP levels among white, African American, Asian, and Hispanic women.[7] Our findings were similar to those from NHANES in that African American women (N = 475, CRP = 2.96 mg/L) were noted to have significantly higher median CRP levels than their white counterparts (N = 24,455, 2.02 mg/L). Additionally, Asian women (N = 357, 1.12 mg/L) had the lowest CRP levels whereas Hispanic women (N = 254, 2.06 mg/L) had CRP concentrations that were similar to those of white women (Figure 1). Interestingly, although body mass index (BMI) was a significant confounder of CRP levels among all racial/ethnic groups, adjustment for measured modifiable risk factors for CVD, including lipid parameters, did not explain the differences in CRP. These data also concur with previous data from large cohorts that demonstrate that CRP levels for women on HRT were higher than for those not on HRT. The proportionate increase in CRP levels in African American women on HRT was similar in magnitude to the increase noted in white women. In contrast, data from 2 smaller studies showed that HRT use was only related to elevated CRP levels among white women.[8,9]

Additional data from NHANES among children aged 3 to 17 years also demonstrate differences in CRP levels by race/ethnicity.[10] The CRP levels of Mexican American children

Figure 1. *Median C-reactive protein (CRP) level and associated interquartile range according to race/ethnic group among participants in the Women's Health Study.*



were significantly higher than the CRP levels of African American, white, and other Hispanic children. Overall, Mexican American and African American children were more likely to have elevated CRP levels. Similar to the finding in adults, BMI was a significant predictor of CRP concentrations. However, there were no reliable relationships among lipid parameters, blood pressure, smoking, and hyperglycemia in children.

The observation that BMI is a crucial contributor to CRP levels among African American and Mexican American women and children parallels the obesity epidemic in the United States that disproportionately affects these 2 racial/ethnic groups. Data from the Centers for Disease Control and Prevention indicate that approximately 78% of African American women and more than 20% of African American and Mexican American children are overweight. These data suggest that low grade excess inflammation starts in childhood and is, at least in part, mediated by BMI. The association between inflammation and overweight status is possibly related to the secretion of tumor necrosis factor a and interleukin-6 (IL-6) by adipose tissue. Unfortunately, although research demonstrates that CRP levels progressively decrease with increasing levels of physical activity and with weight loss, data are virtually nonexistent across racial/ethnic groups.

Metabolic Syndrome, Diabetes Mellitus, and CRP

Because components of the metabolic syndrome, including elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels, elevated systolic blood pressure, and BMI are all associated with increased CRP concentrations, it is not surprising that the metabolic syndrome identifies a high-risk population for CVD. Epidemiologic evidence suggests that CRP levels add prognostic CVD information at all stages of severity of the metabolic syndrome.[11] Given that the prevalence and comparative importance of the components of the metabolic syndrome vary by race/ethnicity, research is needed regarding the relative contributions of blood pressure, HDL cholesterol, tryglyceride levels and BMI to CVD. Data from Duncan and colleagues,[12] regarding race/ethnicity, inflammation, and the development of diabetes demonstrate an association to an inflammation score (comprised of IL-6, CRP, orosomucoid, white blood cell count, fibrinogen, and sialic acid) among Whites (inflammation score – ethnicity interaction, $P = .005$) but not among African Americans. By contrast, data from the Insulin Resistance Atherosclerosis Study (IRAS)[13] demonstrated that the relationship between components of the insulin resistance syndrome and CRP, fibrinogen, and white blood cell count was positive and consistent among non-diabetic white, African American, and Hispanic participants. However, whereas the correlations between CRP and fasting insulin were significant across racial/ethnic groups, the link was not as strong among African Americans as it was for white and Hispanic participants.

Alcohol Intake and CRP

Moderate alcohol intake is associated with reduced cardiovascular events. Both CVD development and CRP levels have a J-shaped relationship with increasing alcohol intake, thereby generating the hypothesis that moderate alcohol intake may attenuate CVD risk, in part by attenuating inflammation.[14,15] Volpato and colleagues analyzed the relationship between race, alcohol intake, and plasma levels of IL-6 and CRP.[16] Similar to published data in Whites, the authors found a J-shaped association between alcohol intake and these markers among African American subjects, suggesting that the relationship between alcohol intake and CRP/IL-6 levels is similar between African Americans and Whites.

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White Blood Cell Count

Some lines of evidence indicate that elevated white blood cell (WBC) count is associated with CVD and all-cause mortality. WBC levels are generally lower in African Americans compared to white individuals, and only a few studies that have looked at the relationship between CVD and WBC count have included African American participants. Using NHANES II data, Brown and coworkers[17] found that even after adjustment for smoking and other risk factors for CVD, individuals with WBC counts greater than 7.6 ($\times 10^9$ cells/L) had a 40% increased risk of coronary heart disease (CHD) death (95% confidence interval [CI], 1.1–1.8) than individuals with a WBC count less than 6.1. However, although this study reported inclusion of approximately 9% African American participants, no racial/ethnic-based data were presented. Other data have

looked at surrogates for CVD such as aortic and carotid plaque thickness. One such study examined the relationship between WBC count and aortic arch plaque thickness in a population of 145 participants, of whom 31.7% were African American and 49.0% were Hispanic. They found that each unit increase in WBC count was associated with an odds ratio of 1.38 (95% CI, 1.05–1.79) for aortic arch plaque thickness greater than or equal to 4 mm, a finding that portends increased risk of stroke.[18] Similar to other data in this field, this study is limited by cross-sectional design and a lack of information about underlying infection in its participants.

Finally, research from the Northern Manhattan Stroke Study population, consisting of 1422 subjects (46.9% Hispanic and 26.7% African American), demonstrated that Hispanics in the highest quartile of WBC count, when compared to those in the lowest quartile, had significantly higher (OR, 2.8; 95% CI, 1.44–5.59) maximal internal carotid artery plaque thickness, a relationship that was not observed among white participants.[19] Among African American subjects in the highest quartile of WBC count, there was an approximate 55% increase in odds of maximal internal carotid artery plaque thickness greater than or equal to 1.9 mm, but the finding failed to achieve statistical significance. These data suggest that any relationship between WBC count and the presence of CVD may differ by race/ethnicity. As the authors note, these data must be interpreted with caution because the sample size of white and African American subjects was smaller than that of Hispanic patients and these findings do not account for ethnic heterogeneity among Hispanics. Generally, data on any relationship between CVD and WBC count have been inconsistent with some studies showing no relationship between these 2 factors after adjustment for potential confounders.

Fibrinogen

Several coagulation factors, including fibrinogen, factors VII and VIII, and plasminogen-activator inhibitor, have been associated with CVD.[20] Furthermore, some data suggest that African Americans may possess different fibrinolytic characteristics than Whites. For example, elderly African Americans in the Cardiovascular Health Study had higher fibrinogen and factor VIII levels than their white counterparts but lower concentrations of factor VII.[21] Similar trends for fibrinogen were noted among young adults, where the highest fibrinogen levels were observed among African American women aged 30 years or older.[22] With the exception of African American men, both white and African American subjects with a family history of heart disease or diabetes tended to have higher plasma levels of fibrinogen. On the other hand, data from the Bogalusa Heart Study[23] demonstrated no significant differences in fibrinogen levels between white and African American children aged 5 to 17 years, although there was a trend towards increased fibrinogen levels with increasing age and Tanner stage in African American females. The reason for the observed higher levels of fibrinogen in African American adults compared to Whites is unclear. Although some of the studies adjusted for smoking, it is possible that additional variables such as BMI, emotional stress, blood pressure and lipid parameters might contribute to observed fibrinogen levels.

Interestingly, whereas African American subjects are generally observed to have higher fibrinogen levels, some data suggest that they have enhanced fibrinolysis. In the Thrombolysis and Angioplasty in Myocardial Infarction trial (TAMI), t-pa antigen levels were noted to be higher among African Americans compared to white patients and African Americans were also noted to have higher coronary artery patency rates.[24] However, in the Thrombolysis in Myocardial Infarction (TIMI) trial, whereas African American participants had higher baseline fibrinogen levels and larger reductions in fibrinogen in response to rt-PA compared to white and Hispanic patients, there was no difference in infarct-related artery patency rates among the 3 racial/ethnic groups.[25] Additional research with adequate cohort sample size is needed to further explore these observations, particularly because the outcome could have a direct impact on the use of therapeutic modalities.

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Adhesion Molecules

Adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), endothelial leukocyte adhesion molecule-1 (E-selectin), and intercellular adhesion molecule-1 (ICAM-1) play a critical role in the recruitment, migration, and binding of circulating inflammatory cells to the vascular endothelium and therefore serve as important mediators of atherosclerotic plaque formation and propagation.

Moreover, experimental data indicate that elevated levels of these molecules are associated with heightened CHD risk. In the Atherosclerosis Risk In Communities (ARIC) Study, an evaluation of the relationship between VCAM-1, E-selectin, and ICAM-1 and carotid atherosclerosis and incident CHD revealed that elevated plasma levels of E-selectin and ICAM-1, but not VCAM-1, were associated with atherosclerotic disease.[26] Of the 792 ARIC participants, approximately 19% were African American and, overall, participants in the highest quartiles of ICAM-1 and E-selectin had 5.53 times the likelihood of CHD and 2.03 times the likelihood of carotid atherosclerosis, respectively, compared to those participants in the lowest quartiles. African American and white subjects had similar associations of ICAM-1 and E-selectin with atherosclerotic disease. However, among African American participants, significantly elevated E-selectin levels were observed only in those persons with incident CHD and carotid atherosclerosis, whereas ICAM-1 levels were significantly elevated in all participants. Furthermore, plasma concentrations of VCAM-1 and ICAM-1 were lower among African American participants than among white participants who did not have CHD or carotid atherosclerosis (control group). The authors speculated that the observed relationship of ICAM-1, but not E-selectin with CHD, might be due to the more prominent role of ICAM-1 in recruiting T cells into unstable lesions or, alternatively, that adhesion molecules may have different roles in multiple arterial sites.

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Conclusion

Data on inflammatory biomarkers among U.S. African Americans are limited by the small numbers of African American subjects enrolled in large epidemiologic cohorts. Although racial/ethnic data on inflammation are beginning to emerge, careful attention must be paid to the impact of environmental factors and socioeconomic issues, in addition to traditional risk factors for CVD, and on the relationship between plasma levels of inflammatory markers and CHD risk. Lessons must be taken from international data on race/ethnicity and inflammation, where differences in CRP and other markers of inflammation have been reported among racial/ethnic groups. The international data on inflammation closely correspond to racial/ethnic relationships between CVD and mortality statistics. For example, CRP levels and ICAM-1 levels have been noted to be significantly lower among black people of African origin (Caribbean and West African) than among white people in England.[27,28] Hence, the heterogeneity of various racial/ethnic groups, as well as the influence of migration, will likely be important confounders of any observed relationship among races/ethnicities. ■

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Main Points

- To date, several markers of inflammation have been evaluated as predictors of cardiovascular disease (CVD); the most extensive and consistent data have been associated with C-reactive protein (CRP).
- Among African Americans, raised CRP levels may be closely linked to body mass index and the obesity epidemic which affects this group disproportionately.
- Evidence from several trials shows African Americans to have higher levels of fibrinogen but also enhanced fibrinolytic characteristics and better response to fibrinolytic therapy when compared to Whites.
- International data on inflammatory biomarkers underscore the heterogeneity of all racial/ethnic groups and show migration and environment to be significant confounders in the relationship between race and levels of biomarkers for CVD.

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