Obesity Associated Inflammation in African American Adolescents and Adults

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Abstract: *Background:* C-reactive protein (CRP) is related to adiposity and metabolic risk and predicts events in adults. The objective was to determine if relationships between adiposity and CRP have similar magnitudes in adolescents as adults. *Methods:* Healthy African Americans (484 adults and 282 adolescents) were recruited from similar environments. In both cohorts, measurements included anthropometrics, blood pressure (BP), metabolic risk factors and inflammatory markers. After stratification by high-sensitivity CRP (hsCRP: ≤1, 1–≤3, >3 mg/dL), adults and adolescents were compared with regard to body mass index (BMI; kg/m^2), waist circumference (WC; cm), BP and other risk factors. hsCRP was regressed on BMI and WC with covariates including cohort, age, sex, BP, insulin resistance, smoking, alcohol and other biomarkers. Interaction terms and a subset of the covariates were subject to a supervised variable selection procedure for a final model. Skewed variables were log transformed and summarized by geometric means (GMs) with 1st and 3rd quartiles (Q1, Q3). *Results:* Among adolescents (16.3%) and adults (34.1%) having high hsCRP(>3 mg/dL), BMI was distributed similarly (GM = 36.4 [32.7, 43.1] and GM = 34.7 [28.8, 40.8], respectively) as was WC (GM = 104.2 [93.0, 119.0] and GM = 104.9 [93.0, 117.2], respectively). In an adjusted regression model, for a given BMI, elevated WC was associated with elevated hsCRP ($P = 0.02$). Although elevated BMI was significantly associated with elevated hsCRP, the relationship was stronger among adolescents (interaction $P = 0.04$). *Conclusions:* These findings demonstrate that, in African Americans, obesity is associated with inflammation and adverse changes in metabolic parameters among both adolescents and young adults.

Key Indexing Terms: Obesity; CRP; Inflammation; Adolescents; African Americans. **[Am J Med Sci 2014;347(5):357–363.]**

The associations between obesity, inflammation and cardiovascular risk are receiving increasing interest. There is now substantial evidence that inflammation contributes to onset and progression of atherosclerosis including plaque development, disruption and thrombosis.[1] C-reactive protein (CRP) is a biomarker of inflammation that mediates multiple effects including upregulation of adhesion molecules, complement binding and decreasing vasodilation by reducing endothelial nitric oxide synthase.[2] Among healthy adults, there is a strong association of CRP with obesity.[3] There is also a strong clinical association of CRP with cardiovascular disease. Among older adults, CRP has been linked to cardiovascular events and mortality.[4] Although less is known about CRP in childhood, some reports from studies in children also describe an association of CRP with obesity and with insulin resistance.[5–7] Investigators from the Cardiovascular Risk in Young Finns study reported that childhood CRP levels were predictive of adult CRP levels.[8] The Pathobiological Determinants of Atherosclerosis in Youth study detected an association between serum CRP levels and raised lesions in the abdominal aorta and right coronary artery, suggesting that CRP could be a biomarker of an early phase of atherosclerosis.[9] Less is known, however, about the strength of the associations of CRP with cardiovascular or metabolic risk factors in childhood, especially among African American youth. In particular, it is not known whether the CRP-obesity relationships among adolescents are similar to that of adults. The purpose of this study was to compare African American adolescents to young adult African Americans with regard to associations between plasma levels of CRP and adiposity. In addition, relationships of CRP to insulin resistance, other inflammatory markers and adiponectin were examined.

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METHODS

Study Samples

Data obtained in 2 separate observational cohort studies were analyzed. A young adult cohort study enrolled African Americans aged 19 to 45 years between 2006 and 2009. African American ethnicity was determined by self-report. All participants were recruited from local communities and were without chronic health problems with the exception of high blood pressure (BP > 130/85 mm Hg) in approximately half of the participants. Obesity, defined as body mass index (BMI) ≥30 kg/m^2, was present in 50% of the cohort. Individuals with known diabetes or other chronic disease were excluded from enrollment. The study protocol was approved by the Institutional Review Board of Thomas Jefferson University. Written informed consent was obtained from each participant at the time of enrollment. The design and method details of the young adult cohort study have been published.[10,11] An adolescent cohort enrolled African Americans aged 13 to 18 years from 2009 to 2011. African American ethnicity was based on self-report by the adolescent participants and their parents. Using a similar design, the adolescent study enrolled participants with and without high BP (≥120/80 mm Hg) and with and without obesity, defined as BMI ≥ 95th percentile. The adolescents were recruited from primary care clinics in Pediatrics and Family Medicine at Thomas Jefferson University and from community primary care practices. Exclusion criteria for adolescent participants were known diabetes, secondary hypertension, stage 2 hypertension, renal disease and other chronic disease. The study and protocol were approved by the Institutional Review Board of Thomas Jefferson University and the A.I. DuPont Hospital for Children. Written informed consent was obtained from 18-year-old participants. For adolescents aged younger than 18 years, consent was obtained from the parent or guardian at enrollment and assent was obtained from the child.

Study Methods

Similar methods and procedures were applied in both cohort studies. Data on health status, medication use and health related behaviors were obtained by self-report from each participant. Clinical assessment consisted of BP and anthropometric measurements (height, weight and waist circumference [WC]). BMI was calculated as weight (kilogram) divided by height squared (square meter). For the adolescent subjects, obesity was defined according to the CDC criteria (http://www.cdc.gov/obesity/childhood/defining.html), which are based on the child's age, sex and BMI. BP measurements were obtained on each subject, by trained research nurses, following a 10-minute rest period in a seated position with feet flat on the floor and back supported. BP was measured by auscultation using a cuff of appropriate size according to the circumference of the right arm. Four separate measurements of systolic BP (SBP) and diastolic BP (DBP) were obtained at each of 2 separate visits. For adolescents with suspected high BP (≥120/80 mm Hg), a 3rd set of BP measurements were obtained. The average of all measures of SBP and DBP was used as the BP value for each participant.

An oral glucose tolerance test (OGTT) was conducted after a 12-hour overnight fast. A fasting blood sample was obtained for plasma glucose, insulin and lipids. Samples of fasting plasma were also prepared and stored for later assay of cytokines including hsCRP, interlukin(IL)-6, plasminogen activator inhibitor (PAI-1), tumor necrosis factor (TNF)-α, TNF-α receptor (TNF-αR) and adiponectin. Following the ingestion of 75 g of glucose solution (Glucola; Ames Diagnostics, Elkhart, IN), blood samples were then obtained at 30, 60 and 120 minutes postingestion and assayed for plasma glucose and insulin concentrations. Plasma glucose concentration was analyzed with the glucose oxidase technique (YS Model 27; Glucostat, Yellow Springs, OH). Plasma insulin concentration was determined with a solid-phase radioimmunoassay (Coat-a-Count; Diagnostic Products Corp, Los Angeles, CA). Coefficients of variation for intra- and interassay variability for glucose and insulin assays were <5%. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA).[12] Higher HOMA values indicate greater insulin resistance. In addition, all glucose and insulin values on each participant's OGTT were used to compute a composite insulin sensitivity index (ISI) according to the equations of Matsuda and DeFronzo.[13] Lower composite ISI values indicate greater insulin resistance. Fasting lipids including total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL) and triglycerides (TGs) were measured using the Hitachi 704 standard enzymatic method in the Lipid Laboratory of Thomas Jefferson University. All assays for the cytokines were performed by enzyme-linked immunosorbent assay in duplicate using commercially available kits. Kits for adiponectin, IL-6, TNF-α, TNF-αR and hsCRP were obtained from R&D Systems (Minneapolis, MN). The kits for PAI-1 were obtained from Aniara (Mason, OH). The coefficient of variation for these assays was consistently <10% and mostly <6%.

Glucose tolerance status was determined using fasting and 2-hour OGTT glucose values: normal glucose tolerance was defined as fasting blood glucose < 100 mg/dL and 2-hour post-OGTT glucose < 140 mg/dL; impaired glucose tolerance was defined as fasting blood glucose 100 to 125 mg/dL or 2-hour glucose of 140 to 199 mg/dL; and diabetic was defined as fasting blood glucose >125 mg/dL or 2-hour post-OGTT glucose >199 mg/dL. Metabolic syndrome for adults was defined according to NCEP/ATP III guidelines.[14] These criteria were modified for adolescents by using ≥120/80 mm Hg for high BP and ≥110 mg/dL for elevated TG.[15]

Statistical Methods

Subjects in each cohort were classified, according to hsCRP level, into 2 groups: low (hsCRP ≤ 1 mg/dL), middle (1 < hsCRP ≤ 3 mg/dL) and high (hsCRP > 3 mg/dL). Categorical and continuous variables in each hsCRP group were compared within and between the adolescent and adult cohorts. Categorical variables were summarized by frequency counts with percentages. Continuous variables were summarized by arithmetic means with standard deviations or, if skewed, were log transformed and summarized by geometric means (GMs) with 1st and 3rd quartiles. Study variables were tabled and compared across hsCRP and cohort groups. Student's t tests or ANOVA F-tests were used to evaluate differences in means and Fisher's exact tests were used to evaluate differences in proportions. Adjustments were made to P values to help control the overall false discovery rate.[16] The significance level was set at $\alpha = 0.05$.

A multivariable regression model for hsCRP was determined by application of a 2-staged supervised selection process. In the 1st stage, log-transformed hsCRP was regressed on BMI and WC with covariates including cohort (ie, an adolescent cohort indicator), age, sex, BP, hypertension medication, smoking and alcohol consumption. In the next stage, linear terms for insulin resistance (log HOMA) and biomarkers (including adiponectin, log IL-6, PAI-1, log TNF-α and log TNF-αR) and their respective 2-way cohort interaction terms and respective 2-way cohort interaction terms with BMI, WC, SBP and gender were either removed or selected to remain in the 1st stage model by the hybrid least angle regression method.[17] All continuous covariates were mean centered before modeling. Antilogged regression coefficients, representing geometric mean ratios (GMRs), with 95% confidence intervals and P values from the selected model are presented.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 505 African American adults were enrolled in the study. Of these, complete data for this analysis were available on 484 subjects. For the adolescent cohort, a total of 301 African American adolescents were enrolled. Of these, complete data were available for this analysis on 282 adolescents. When comparing adolescents and adults, we found that, on average, hsCRP was 47% lower among adolescents (GM, 0.78 versus 1.66). However, when the cohorts were stratified by hsCRP level, more complicated relationships become apparent. Table 1 provides the plasma hsCRP GM in each adolescent and adult hsCRP group and the clinical and demographic characteristics, by categorical variable, of each group. GM hsCRP plasma level was similar for adolescents and adults in the middle (GM hsCRP, 1.79 versus 1.74) and high (GM hsCRP, 5.19 versus 5.17) hsCRP groups. Among the adolescents, 16.3% (N = 46) of the cohort had high hsCRP (≥3 mg/dL), compared with 34.1% (N = 165) having high hsCRP in the young adult cohort. Gender was similarly represented in the hsCRP groups among adolescents and adults, with female gender being more frequent among high versus low hsCRP groups. Metabolic syndrome was also similarly represented in the hsCRP groups among adolescents and adults. Figure 1 depicts the log-transformed hsCRP values among individuals with and without metabolic syndrome in both cohorts. Among those without metabolic syndrome, hsCRP tended to be lower among adolescents compared with adults. Among those with metabolic syndrome, hsCRP was distributed similarly in both adolescents and adults and was higher than those without metabolic syndrome. Accordingly, the distribution