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Diverging trajectory patterns of systemic versus vascular inflammation over age in healthy Caucasians and African-Americans

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ABSTRACT

Objective: Age and inflammation are risk factors for cardiovascular disease but the impact of inflammation on cardiovascular risk across the lifespan is not understood. We investigated whether an inflammatory burden is modulated by age in healthy subjects.
Methods: Caucasian and African-American families were recruited from the general population (age range: 6–74 years, n = 267). Systemic inflammation was assessed by C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin and α-acid glycoprotein, and vascular inflammation was assessed by pentraxin-3 (PTX-3), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM). To collectively assess systemic or vascular factors across the age spectrum, a composite z-score for each marker category was calculated.
Results: There was a contrasting pattern in systemic versus vascular inflammatory burden over age with an increase in systemic but a decrease in vascular markers in both ethnic groups. The results remained unchanged after adjustments for the covariates and covariance. When looking at individual markers to examine which markers are most contributing factors to the composite scores, CRP and SAA were significantly and positively associated with age, while PTX-3 and sVCAM were significantly and negatively associated with age in both ethnic groups.
Conclusions: The composite z-score for systemic inflammation increased with age, while the composite z-score for vascular inflammation declined with age, irrespective of ethnicity. The findings illustrate a regulatory relationship between age and inflammation, and suggest that a perceived elevation of vascular markers among the very young may be an indication of physiological changes rather than reflecting a disease process.

1. Introduction

Inflammation plays a key role in the atherosclerotic process [1] and studies have demonstrated a positive association between risk for cardiovascular disease (CVD) and levels of inflammatory markers [2–7]. Some markers [high sensitive C-reactive protein (CRP), serum amyloid A (SAA) or fibrinogen] reflect a more systemic inflammatory burden [8–10], whereas others are considered more informative with regard to local injuries such as vascular inflammation and endothelial dysfunction [11–17]. These two types of biomarkers, systemic versus vascular, tend to correlate weakly with each other, suggesting different underlying pathophysiological mechanisms. Furthermore, there are ethnic differences in inflammatory biomarker levels in adults, potentially related to demographic or lifestyle-related factors [18]. Previously, we have shown heterogeneity in the relationship of systemic versus vascular inflammatory markers with age among middle-aged Caucasian and African-American adults undergoing coronary angiography [19].

Increasing evidence now supports the concept that the roots of chronic diseases, such as CVD, occur early in life with disease progression accelerating gradually through childhood and adolescence leading to CVD in adulthood [20]. Inflammation, a key feature

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of CVD, may underlie such processes, resulting in the rise of adult disease manifestations in children. In support of this concept, a low-grade inflammation measured by elevated levels of CRP was present in children with detectable differences between ethnic groups [21]. However, there is limited information available with regard to the distribution and trend patterns of different inflammatory markers across the lifespan in the general population. It is unclear if the heterogeneity in inflammatory burden between systemic and vascular markers over an age spectrum would be present in healthy individuals. To address these questions, we measured two sets of markers, one set representing general systemic inflammation [CRP, SAA, fibrinogen, haptoglobin (HPTG), and α-acid glycoprotein (AGP)] and another set representing vascular-focused inflammation [pentraxin-3 (PTX-3), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1)] and assessed the trajectory patterns of these markers across an age spectrum in Caucasian and African-American subjects. In order to attenuate the potential contribution of genetic or environmental factors, we recruited members of the same families across ages, i.e., parents and their children.

2. Materials and methods

2.1. Human subjects

Caucasian or African-American families with minimum of two biological children at least six years old were eligible to participate in the study. Families were recruited from the general population in the city of Sacramento and surrounding California counties by advertisement. Healthy subjects responding to advertisement were invited to the Clinical Research Center of the University of California Davis Clinical and Translational Science Center for a medical history questionnaire, physical examination and blood draws. Being healthy was defined for the purpose of the present study as not having any chronic medical condition under treatment by a pediatrician or a family physician, other than high blood pressure, high lipids or seasonal allergies. There were no subjects with intercurrent infections at the time of observation. Information on demographics and medical history using a standardized questionnaire and anthropometrics were obtained. Non-fasting blood was collected and plasma was stored at −80°C until analyses.

We recruited a total of 82 families (60 Caucasian and 22 African-American) where each family had at least two biological children (≤18 years of age). Race/ethnicity was self-reported for each individual family member with use of a questionnaire as Asian/Pacific Islander, White, Native American/Alaskan Native, African-American, or Hispanic. A few families had an admixture of ethnic backgrounds with some members identifying several ethnicities. Based on the self-selection, we classified subjects into three categories: a) Caucasian; b) African-American; and c) Other. There were a total of 327 subjects, 182 self-identified as Caucasians, 87 as African-Americans, and 58 as Others. Two children (one Caucasian and one African-American) were excluded due to missing blood sample. The present report is based on findings in 181 Caucasians and 86 African-Americans. The study was approved by the Institutional Review Board at the University of California Davis and informed consent was obtained from all subjects. Minors were asked to give their assents (Assent form for 12–17 years old; or Letter of information for 8–11 years old), and one of the parents signed the consent forms for their children.

2.2. Clinical and biochemical assessment

Blood pressure (BP) was measured with a random-zero mercury sphygmomanometer. Body mass index (BMI) was calculated as body weight (kg) divided by squares of height (m^2). For children and adolescents (six to 20 years), BMI-for-age growth charts for either boys or girls (Center for Disease Control and Prevention) were used to obtain a percentile ranking [22]. Concentrations of total cholesterol (TC), HDL cholesterol (HDL-C), triglycerides, apolipoprotein (apo) B-100, apoA-1, and glucose were measured using standard procedures. LDL cholesterol (LDL-C) concentrations were calculated with the formula of Friedewald et al. [23]. Plasma fibrinogen concentration was determined at the University of California Davis chemical laboratory. Concentrations of high-sensitivity CRP, HPTG and AGP were measured using Human CVD Panel 3 (Acute Phase) Magnetic Bead Panel Kit assays with manufacturer's recommended equipment and setting (#HCVD3MAG-67K, Milliplex Map, EMD Millipore, Billerica, MA). Similarly, concentrations of SAA, sICAM-1, and sVCAM-1 were determined by Human CVD Panel 2 Magnetic Bead Panel Kit (#HCVD2MAG-67K, Milliplex Map, EMD Millipore, Billerica, MA). PTX-3 concentration was assessed by ELISA using a commercially available kit (Enzo Life Sciences. Inc., Plymouth Meeting, PA) [19,24]. Analyses were run according to the manufacturers' specifications in duplicate samples with two different quality controls, which were within the recommended precision for each test. Coefficients of variation of inflammatory markers were consistently less than 7%.

2.3. Statistics

Statistical analyses of data were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Results were expressed as mean ± standard error of mean, or median with interquartile range for non-normally distributed variables. Values of triglycerides, glucose, CRP, fibrinogen, SAA, HPTG, AGP, PTX-3, sICAM-1, and sVCAM-1 were logarithmically transformed to achieve normality for statistical inferential analyses. Proportions were compared between groups using χ^2 test or Fisher's exact test as appropriate. Group means were compared using Student's t-test. Differences in individual markers for each group by age and race/ethnicity were assessed by an Analysis of Variance (ANOVA). Multiple testing was corrected by the Tukey's Honestly Significant Difference (HSD) procedure to maintain the family-wise Type I error rate at 0.05. To construct a composite score of multiple markers, we first calculated a z-score for each inflammatory marker [$z = (x - \bar{x})/SD$, where x is an individual marker value, $\bar{x}$ is the mean marker value, and SD is the standard deviation of marker values] as previously described [19]. Using the individual z-scores, we next calculated a composite z-score for systemic inflammation [i.e., z-score (systemic) = Average (z-CRP, z-fibrinogen, z-SAA, z-HPTG, z-AGP)], and for vascular inflammation [z-score (vascular) = Average (z-PTX-3, z-sICAM-1, z-sVCAM-1]. Mixed-effects regression models were used to estimate patterns of marker scores as a function of age and to test the effects of race/ethnicity and covariates on the patterns of marker scores in relation to age. All core models included fixed effects for race/ethnicity, the linear effect of age, and the interaction between race and age, with covariates for multivariate models. To account for the correlated nature of the data among members from the same family, the mixed-effects models included two random effects for family-specific intercepts and slopes. Two-tailed *p*-values less than 0.05 were considered statistically significant.

We originally aimed to assess the relationships between age and inflammatory markers, adjusting for covariates. Based on our previously published study of various inflammatory markers and after reviewing various partial correlations between age and composite scores of systemic and vascular inflammation, controlling for covariates (Table 3 of Reference 3), we surmised that the true partial correlations would be likely to be at least 0.35 and 0.24 for systemic and vascular inflammation, respectively. We used an