Published in final edited form as:

J Cardiovasc Med (Hagerstown). 2014 May ; 15(5): 371–376. doi:10.2459/JCM.0b013e32836411d6.

C-reactive Protein and Subclinical Cardiovascular Disease among African Americans: (the Jackson Heart Study)

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Abstract

Objective—Systemic inflammation has been implicated as an early marker for subclinical cardiovascular disease; however, findings have been inconsistent in the African American population.

Methods—We examined the relation of C-reactive protein to subclinical disease in African American participants of the Jackson Heart Study first examination. Subclinical disease evaluated included aortic valve calcification (AVC), carotid intima-medial thickness (IMT) and peripheral arterial disease (PAD). We assessed the relation of C-reactive protein to subclinical disease adjusting for age, body mass index, sex, systolic and diastolic blood pressure, diabetes, total/HDL cholesterol, triglycerides, smoking, antihypertensive therapy, lipid lowering therapy, and hormone replacement therapy.

Results—In the study population approximately, 5.1% of participants had AVC and 6.7% had PAD. In the age- and sex- adjusted model, CRP was significantly related to AVC ($p=0.02$) and carotid IMT ($p=0.02$). However, in the multivariable-adjusted logistic regression analysis, C-reactive was significantly related to AVC ($p=0.02$) and to PAD ($p=0.04$) but not to carotid IMT ($p=0.18$).

Conclusion—We describe significant associations between C-reactive protein and AVC and PAD in a population-based cohort of African Americans.

Keywords

CRP; Subclinical disease

Introduction

C-reactive protein (CRP) is the biomarker that has been the most widely studied in relating systemic inflammation to subclinical atherosclerotic disease and has proven to be useful tool in better understanding the pathogenesis of atherosclerosis. It is considered a potential biomarker for progression of subclinical cardiovascular disease.(1–3)

The large community-based cohort of African Americans recruited in the Jackson Heart Study provides a unique opportunity to study the role of system inflammation in the development and progression of subclinical atherosclerosis in this high risk population with a high burden of cardiovascular mortality.(4–6) In this study, investigators evaluated the relation of CRP with aortic valve calcification (AVC), carotid intima-medial thickness (IMT) and peripheral arterial disease (PAD) [as defined by ankle-brachial index (ABI)] in a large cohort of middle-age and older African Americans. We hypothesize that higher concentrations of CRP are significantly associated with subclinical disease in this population after adjusting for traditional risk factors. Findings from this study may further our understanding of the role of systemic inflammation in the pathogenesis of atherosclerosis in African Americans and how that may relate to higher cardiovascular outcomes.

Methods

Study Population

The design and recruitment methods for the Jackson Heart Study cohort have been previously described.(7, 8) Among the 5,301 participants in the Jackson Heart Study recruited for Examination one, 100 participants were excluded due to missing CRP, 591 participants were excluded due to missing covariates and 486 participants were excluded due to prevalence of cardiovascular disease. Therefore, there were 4,124 participants in our study population to describe the demographic and clinical characteristics. In order to analyze subclinical disease, there were three different sample populations. There were 240 participants excluded due to missing information on AVC, 604 excluded due to missing PAD data and 200 excluded due to missing information on carotid IMT. Therefore, there were 3,884 participants in the population used to analyze the relation of CRP with AVC, 3,520 participants used to analyze the relation of CRP with ABI-defined PAD, and 3,924 participants used to analyze the relation of CRP to carotid IMT.

C-reactive protein and Subclinical Disease—Methods for measuring C-reactive protein concentrations and covariate data in the Jackson Heart Study have been previously described.(9) Briefly, CRP was assessed by the immunoturbidimetric CRP-Latex assay using a Hitachi 911 analyzer. The interassay coefficients of variation on control samples and the reliability coefficient for masked replicates were 4.5% and 95%, respectively.

In the Jackson Heart Studies, the aortic valve was assessed on echocardiogram examinations performed by one of four experienced sonographers using a 2.5 - 5 MHz transducer mounted on a Sonos 4500 Hewlett Packard ultrasound machine. Sonographers were blinded to clinical information, and measurements were over-read by one reader. AVC was defined as

visible valvular thickening and nodular calcification and an antegrade peak velocity of less than 2.5 m/s.

To determine ABI-defined PAD, two ankle systolic BP measurements were taken on each leg while the participant was in the supine position. Measurements of the brachial systolic BP, usually in the right brachial, were taken twice. Two ABIs (one for the right leg and one for the left leg) were calculated as the average of the two ankles' systolic BP measurements divided by the average of the two brachial readings. The lower of the two ABIs were considered the ABI for the participant for the current study. To exclude falsely high ABIs due to arterial non-compressibility, ankle BP values that were 75 mmHg above the brachial systolic BP were excluded. Participants were considered to have ABI-defined PAD if the $ABI < 0.9$.

Using the 7.5 MHz transducer mounted on the Sonos 4500 Hewlett Packard, three segments of the carotid artery were imaged bilaterally to obtain carotid IMT measurements: the distal 1-cm portion of the common carotid artery, the 1-cm portion of the carotid bifurcation distal to the tip of the flow divider, and the 1-cm portion of the internal carotid immediately proximal to the tip of the flow divider. All segments were imaged from the optimal angle (the interrogation angle most clearly showing the tip of the flow divider). Two additional circumferential images were collected from each common carotid artery, selected to ensure that one anterior, lateral and posterior image were collected bilaterally. All images were recorded to video cassette for off-line processing. For each participant, mean far wall IMT for each vessel segment were measured from leading edge to leading edge by one of two certified readers. Readers also recorded the presence or absence of plaque for each image, with plaque defined based on the presence of at least two of the following criteria: focal thickening, surface irregularity or heterogeneity of echo intensity.

Statistical Analyses

Descriptive statistics (mean $\pm$ standard deviation or percentages) were computed for demographic and clinical characteristics by quartile of CRP. Since its distribution was skewed, CRP was natural log-transformed for clinical correlates analyses. For the analysis, AVC, PAD, and carotid IMT were analyzed as dichotomous variables. For determining carotid IMT, maximum likelihood techniques for linear models were used to calculate reader and time adjusted IMT summary measure that is the average far wall IMT of the common, bifurcation and internal carotids, bilaterally, at the optimal angle of interrogation (subsequently referred to as carotid IMT). For this analysis, participants whose summary measures were in the upper 10th percentile of carotid IMT were compared to participants whose summary measures were in the lower 90th percentile. The upper 10th percentile of carotid IMT for this study population corresponded to a thickness of 1.0 mm (in the ARIC study, $IMT > 1.0$ mm was predictive of incident stroke).⁽¹²⁾ The likelihood ratio statistic was performed to examine the linear trend for continuous variables. For categorical variables, the Cochran-Armitage test is used. Age-sex adjusted logistic regression and multivariable logistic regression were performed to assess the relation of CRP with AVC, CRP with carotid IMT and CRP with PAD, adjusting for cardiovascular disease risk factors including age, sex, BMI, systolic and diastolic blood pressure, diabetes, total/HDL

cholesterol, triglycerides, smoking, antihypertensive therapy, lipid lowering therapy, and hormone replacement therapy. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Three study populations had the same age and gender distributions (mean age: 55 years old, female: 64%). In general, approximately 5.1% of participants had AVC and 6.7% had PAD.

The distribution of clinical characteristics by quartile of CRP is shown in Table 1. Greater age, female sex, higher BMI, higher systolic and diastolic BP, worse lipid profile, higher waist circumference, diabetes status, smoking status, hormone replacement therapy in women and hypertension medication were all related higher quartiles of CRP. Lipid lowering therapy was not associated with quartile of CRP.

Figure 1 shows the age and sex adjusted distribution of subclinical disease by quartile of CRP. In general, a higher percentage of participants in the third and fourth quartile of CRP had evidence of AVC by echocardiogram and evidence of PAD by ABI compared to participants in the first and second quartiles of CRP. However, there was less of a progressive positive trend between quartiles of CRP and carotid IMT. The percent of participants with measures of carotid IMT in the top decile was > 1.5 fold higher in the second quartile of CRP than in the first quartile of CRP. However, the percentage in the top decile were slightly less in the third and fourth quartiles of CRP.

Table 2 shows the results of the age- and sex-adjusted and multivariable-adjusted models assessing the relation of CRP with AVC, ABI-defined PAD and carotid IMT. In the age- and sex- adjusted model, CRP was significantly related to AVC ($p=0.02$) and carotid IMT ($p=0.02$). However after controlling for age, sex, body mass index (BMI), systolic blood pressure, diabetes, total: HDL cholesterol, smoking, and antihypertensive therapy in the multivariable-adjusted model, CRP was significantly related to AVC($p=0.02$) and PAD ($p=0.04$) but not IMT ($p=0.18$)

Discussion

Principal Findings

CRP, a marker of systemic inflammation, was significantly related to subclinical atherosclerosis in a population-based cohort of middle-aged and elderly African Americans. The higher the CRP, the more likely participants had evidence of AVC on echocardiogram and the more likely participants had ABI-defined PAD. These findings suggest that elevated CRP in part reflect the burden of atherosclerosis in African Americans.

Subclinical Disease in African Americans

In this community-based cohort of African Americans we found that AVC, ABI-defined PAD were 5.1% and 6.7% respectively. We also found that traditional risk factors were significantly related to all three forms of subclinical disease (AVC, PAD and carotid IMT).

AVC was slightly less prevalent in the JHS than in other studies of African Americans. In the ARIC study, approximately 8% of participants had AVC compared to approximately 5% in this study. Differences in ultrasound between the two cohort examinations and age differences between the cohorts (the ARIC group was somewhat older) may account for the differences in prevalence. In both studies, AVC was significantly associated with age, male sex, systolic blood pressure, diabetes, and the presence of carotid artery disease. However in the JHS cohort, systemic inflammation and participant's lipid profile were not significantly related to AVC.(13)

As with AVC, ABI-defined PAD has been related strongly to traditional risk factors.(14, 15) ABI defined PAD has been found to be more prevalent in African Americans in racially mixed cohorts. For example, in NHANES after adjustment for traditional CVD risk factors, it was found that the odds of having PAD were 1.5-fold higher in African Americans than in non-Hispanic whites, Hispanics and Chinese.(16–18) The prevalence in African Americans was 7.9% (similar to our estimated rate of approximately 7%). Similarly, carotid IMT was significantly related to traditional cardiovascular risk factors in our study, similar to that seen in other large cohorts that included racially mixed populations of both younger and older participants.(19, 20) All of these factors were significantly associated with carotid IMT in our cohort as well.

Previous Studies Relating CRP to Subclinical Disease

There is conflicting evidence linking systemic inflammation to subclinical disease in the general population and there is very limited information of the link to date in African Americans. In this study of the Jackson Heart Study cohort, there was no relation between CRP and carotid IMT after adjusting for multiple risk factors. In the Framingham Heart Study, among participants who received a CRP measurement at baseline and then underwent carotid ultrasonography 4 years later, there was a graded association between CRP and carotid atherosclerosis in women but not in men. In another study of middle-aged women from the general population, CRP was only weakly associated with common carotid artery IMT and this relationship was limited to ever-smokers.(22) In the Young Finns Study, the association between CRP and CIMT was due largely to obesity and BMI.(23) In the current study, investigators found that potentially BMI played a significant role in the relation between CRP and carotid IMT in our cohort.

In our study, plasma CRP was significantly related to PAD in the Jackson cohort. Ridker et al, in the Physicians' Health Study, found significantly higher CRP levels at baseline predicted those who subsequently developed symptomatic PAD over 5 years.(14) In a prior study, CRP was also found to predict a poorer lower extremity performance in those with PAD.(24) In some conflict with the these investigations, another study of 370 patients with and without PAD, found an independent association between CRP and ABI was limited to participants with a history of cardiac or cerebrovascular disease.(25)

Finally, in our study of middle-aged and elderly African Americans, we found a significant relation between plasma CRP levels and the presence of AVC on echocardiogram. There are limited number of studies that have examined the relation of CRP to AVC though recent investigations suggest a link with systemic inflammation using CRP as a biomarker.(26–28)

In general, findings to date suggest that CRP, as a product of the inflammatory process, may be a biomarker for early atherosclerosis. This study extends the finding to a community-based group of African Americans.

Mechanism Relating C-reactive Protein to Subclinical Cardiovascular Disease

C-reactive protein may be both a marker of CVD and an active participant in the disease process. Inflammation appears to characterize the lesions of atherosclerosis at all stages of disease.(29) There is tissue evidence that systemic inflammation plays a role in subclinical disease. Recently, Skowasch et al, observed localization of CRP in aortic valve tissue.(30) In this study, CRP showed a significant correlation with aortic valve CRP expression. These findings have been further supported by in vitro evidence showing that exposure of the aortic wall to CRP simulate increased AVC.(31)

It is plausible that the CRP genotype influences the synthesis of CRP by the liver thereby affecting levels of plasma CRP and the risk of early-onset atherosclerosis.(32) In investigations studying systemic inflammation relation to integrity of the arterial intima, CRP has been found in atherosclerotic plaques supporting its potential involvement in the development of atherosclerosis.(33) CRP appears to affect vascular health through the amplification of local inflammation (through the attraction and accumulation of macrophages, mast cells, and activated T cells along the vessel wall) that leads to the initiation and progression of the atherosclerotic lesion.(34)

Clinical implications

In our study cohort of middle-aged to elderly African American men and women, higher levels of CRP were associated with aortic valve calcification, peripheral artery disease and carotid IMT in non-obese participants. Our findings support the theory that chronic inflammation is related to early atherosclerosis and extends the theory to include African Americans.(21, 35) Clinically, our findings suggest that CRP can be used as a marker for atherosclerotic burden in African Americans. Additionally, these findings may help explain the relation that CRP has to those with increased risk of cardiovascular events as seen in the Physicians' Health Study.(36) What is not known and still warrants investigation is whether CRP may serve as a target for prevention and management of subclinical and clinical atherosclerotic disease in this group.

Limitations

We are observing cross-sectional relations and therefore cannot demonstrate whether CRP leads to subclinical, subclinical leads to increased CRP or whether they are both related to a third unaccounted for risk factor. Also prevalent CVD was by self-report so there is potential for misclassification. Although we viewed AVC, carotid IMT, and ABI-defined PAD as markers of subclinical atherosclerotic disease, translation of these phenotypes to represent overall atherosclerotic burden should be done cautiously, as rates of progression to disease may differ in different vascular territories. Finally, the results of this study may not be generalizable to other populations and in atherosclerosis in other major vascular beds.

Conclusions

We demonstrated that CRP concentration is associated with AVC and ABI-defined PAD after adjustment for several traditional CVD risk factors. The present finding suggest a strong relation between CRP and atherosclerotic disease in African Americans and support the hypothesis that systemic inflammation is related to atherosclerotic disease burden in this group.(14) It is not known however whether plasma CRP concentrations increase as subclinical disease progresses. Further studies are needed to answer this question, as well as to determine whether treatments with agents that have anti-inflammatory properties (such as aspirin or statins) may lower plasma CRP and slow progression of subclinical disease in African Americans.

Acknowledgments

Funding

The Jackson Heart Study (JHS) is a collaborative study supported by the National Institutes of Health and the National Center on Minority Health and Health Disparities (study ID numbers: 5001; N01 HC95170; N01 HC95171; N01 HC95172) in partnership with three local institutions (University of Mississippi Medical Center, Jackson State University and Tougaloo College). Dr. Fox's work on this project is supported by American Heart Association (0555209B). Dr. Jae Eun Lee's work on this project is supported by NIMHD (U54MD008149).

The authors thank the staff and participants in the JHS for their important contributions.

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Figure 1.

Age-Sex Adjusted Distribution of Subclinical Disease by Quartile of CRP

AVC, aortic valve calcification; PAD, peripheral arterial disease

CIMT; carotid intima medial thickness, CRP, C-reactive protein

Q1, Q2, Q3, Q4, - first, second third and fourth quartile of C-reactive protein

Percentage % represents the percent of participants with subclinical disease (aortic valve calcification, peripheral artery disease or upper 10th percentile of sum carotid intimal thickening) within the quartile

Table 1

Demographics of Study Population by Quartile of CRP

	CRP Q1	CRP Q2	CRP Q3	CRP Q4	p linear trend
	(0–1.05)	(1.06–2.60)	(2.61–5.51)	(5.52–338.0)	
n	1033	1025	1018	1022	
Age, years	52.3(13.4)	54.3(13)	54.6(12.4)	54(12.1)	0.003
Body mass index, kg/m ²	27.8(5)	30.6(5.9)	32.3(6.5)	36.3(8.5)	<.0001
Systolic blood pressure, mmHg	123.9(17.7)	127.5(18)	127.6(18.1)	126.5(17.8)	0.0015
Diastolic blood pressure, mmHg	79.4(10.4)	79.9(10.4)	79.1(10.5)	77.8(10.3)	0.0002
HDL-total cholesterol ratio	3.9(1.2)	4.2(1.3)	4.2(1.4)	4.1(1.4)	0.0324
Triglycerides, mg/dL	90.6(59.2)	110.3(76.1)	118.7(134.4)	112(85.8)	<.0001
Waist Circumference, cm	92.3(13.4)	98.7(14.2)	102.3(15.1)	108.4(18)	<.0001
C-reactive protein, mg/L	0.5(1.9)	1.7(1.3)	3.8(1.2)	11.1(1.8)	<.0001
Female, %	49.4	56.7	69.3	83.2	<.0001
Diabetes, %	11.2	14.5	19.8	19.6	<.0001
Smoking, %	11	11.2	12.8	14.4	0.0144
Antihypertensive medications, %	36	46	52.2	56.3	<.0001
Lipid lowering medications, %	11.1	11	11.6	9.3	0.2509
HRT medications, %	15.1	16.5	24.8	28.5	<.0001
Hypertension, %	49.2	58.1	62.9	66.5	<.0001

HRT, percent of women on hormone replacement therapy

Q1, Q2, Q3, Q4 – first, second, third and fourth quartile of c-reactive protein

Table 2

Relation of C-Reactive Protein to Three Measures of Subclinical Disease

Aortic Valve Calcification	Geometric Mean $\pm$ SE	β^{**}	p-value^{**}
Age- and sex-adjusted		0.1720	0.01
No aortic valve calcification	2.2 $\pm$ 1.0		
Aortic valve calcification	2.6 $\pm$ 1.1		
Multivariable-adjusted [*]		0.1928	0.01
No aortic valve calcification	2.2 $\pm$ 1.1		
Aortic valve calcification	2.6 $\pm$ 1.1		
Peripheral Artery Disease			
Age- and sex-adjusted		0.0756	0.23
No peripheral artery disease	2.1 $\pm$ 1.0		
Peripheral artery disease	2.3 $\pm$ 1.1		
Multivariable-adjusted [*]		0.1399	0.04
No peripheral artery disease	2.1 $\pm$ 1.1		
Peripheral artery disease	2.5 $\pm$ 1.1		
Carotid Intima Medial Thickness			
Age- and sex-adjusted		0.1162	0.02
Lower Carotid IMT	2.2 $\pm$ 1.0		
Upper Carotid IMT	2.5 $\pm$ 1.1		
Multivariable-adjusted [*]		0.0779	0.18
Lower Carotid IMT	2.2 $\pm$ 1.1		
Upper Carotid IMT	2.4 $\pm$ 1.1		

^{*} adjusting for age, sex, body mass index (BMI), systolic blood pressure, diabetes, total/HDL cholesterol, triglycerides, smoking, antihypertensive therapy, lipid lowering therapy, and hormone replacement therapy

^{**} β and p-value from logistic regression model