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Association of inflammatory markers with subclinical atherosclerosis in middle-aged white, Japanese-American, and Japanese men: the ERA-JUMP Study

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Conflict of interest

The authors declared no conflict of interest.

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Abstract

Aim—To examine whether the inflammatory markers, C-reactive protein (CRP) and fibrinogen, are associated with biomarkers of atherosclerosis [carotid intima-media thickness (IMT) and coronary artery calcification (CAC)] in the general male population, including Asians.

METHODS—Population-based samples of 310 Japanese, 293 Japanese-American and 297 White men aged 40-49 years without clinical cardiovascular disease had IMT, CAC, CRP and fibrinogen levels, and other conventional risk factors measured using standardized methods. Statistical associations between the variables were evaluated using multiple linear or logistic regression models.

RESULTS—The Japanese group had significantly lower levels of inflammatory markers and subclinical atherosclerosis than the Japanese-American and White groups (*P*-values all <0.001). The mean levels of CRP were 0.66 vs. 1.11 and 1.47 mg/L, and fibrinogen 255.0 vs. 313.0 and 291.5 mg/dl, respectively. Mean carotid IMT was 0.61 vs. 0.73 and 0.68 mm, and the prevalence of CAC 11.6% vs. 32.1% and 26.3%, respectively. Body mass index (BMI) showed significant positive associations with both CRP and fibrinogen levels. Although CRP showed a significant positive association with IMT in Japanese men, this association became non-significant after adjustment for traditional risk factors or BMI. In all three populations, CRP was not associated significantly with the prevalence of CAC. Similarly, fibrinogen did not show a significant association with either IMT or the prevalence of CAC.

CONCLUSIONS—The associations of inflammatory markers with subclinical atherosclerosis may merely reflect the strong association of BMI with inflammatory markers and subclinical atherosclerosis in both Eastern and Western populations.

Keywords

obesity; C-reactive protein; fibrinogen; intima-media thickness; coronary artery calcification

INTRODUCTION

It is well established that inflammation plays a pivotal role in atherogenesis, with inflammatory markers such as C-reactive protein (CRP) and fibrinogen shown to be useful for detecting individuals at higher cardiovascular risk.[1-7] Subclinical atherosclerosis characterized by increased intima-media thickness (IMT) or coronary artery calcification (CAC) has been reported to independently predict future cardiovascular events.[8-10] However, evidence on the relationship between inflammatory markers and subclinical atherosclerosis is inconsistent. Although two meta-analyses showed positive associations of IMT with CRP and fibrinogen,[11,12] other studies did not show this association after adjustment for traditional cardiovascular risk factors including measures of adiposity.[13-15] On the other hand, a small number of studies have reported a relationship between CAC and inflammatory markers. However, the majority of these studies showed no significant relationships after adjustment for traditional risk factors, especially measures of

adiposity,[12,16-18] although two studies showed that fibrinogen, but not CRP, was weakly and independently associated with CAC.[19,20]

It also remains to be elucidated whether the effect of inflammatory markers on atherosclerosis differs in various populations with different genetic or environmental backgrounds. To our knowledge, no previous study has examined the relationship between inflammatory markers and CAC in Asian general populations living in Asia, including Japanese populations.

We have previously reported the levels of subclinical atherosclerosis (i.e., CAC and IMT) in population-based samples of 868 men aged 40-49 years (281 Japanese living in Japan and 281 Japanese Americans and 306 Whites living in the USA) from the Electron-Beam Tomography, Risk Factor Assessment Among Japanese and U.S. Men in the Post-World War II Birth Cohort (ERA-JUMP) Study.[21] Using data collected in that study we examined whether the inflammatory markers, CRP and fibrinogen, were associated with subclinical atherosclerosis evaluated using CAC and IMT in three general middle-aged populations; Japanese men living in Japan, and Japanese-American men and White men living in the USA.

METHODS

Design

We analyzed the data from the ERA-JUMP study, a population-based, multi-center, cross-sectional study of 904 men aged 40 to 49 years. The study was characterized by highly standardized methods to measure subclinical atherosclerosis and all other variables.

Study participants

The details of the study population have been described previously.[21,22] Between 2002 to 2006, 926 men aged 40 to 49 years were selected randomly for enrollment in the study. The study group enrolled included 313 Japanese men from Kusatsu, Shiga, Japan, 310 White men from Allegheny County, Pennsylvania, and 303 Japanese-American men from a representative sample of offspring of fathers who participated in the Honolulu Heart Program, Honolulu, Hawaii.[23] These offspring were third or fourth generation Japanese Americans without ethnic admixture. At baseline, all the participants were without clinical cardiovascular disease, type 1 diabetes, or other severe diseases. We excluded 27 participants with missing data, leaving a final study group that included 310 Japanese, 293 Japanese-American, and 297 White men. Informed consent was obtained from all the participants. The study was approved by the Institutional Review Boards of Shiga University of Medical Science, University of Pittsburgh, and Kuakini Medical Center.

Data collection

Body mass index (BMI) and blood pressure (BP) were measured using standardized methods as described previously.[21,22] Fasting glucose and serum lipid levels, including low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were also determined as described previously.[21,22] Diabetes mellitus was

defined as the use of anti-diabetic medication(s) or a fasting glucose ≥ 7.0 mmol/L (126 mg/dL). Hypertension was defined as the use of anti-hypertensive medication(s) or a systolic/diastolic BP ≥ 140/90 mmHg. CRP was determined using a calorimetric-competitive-enzyme-linked-immunosorbent assay and fibrinogen by an automated-clot-rate assay (Diagnostica Stago, Parsippany, NJ, USA). The serum samples were stored at –80°C and shipped on dry ice to the University of Pittsburgh for testing. The coefficient of variation for CRP and fibrinogen was 2.71 and 2.46%, respectively.

Self-administered questionnaires were used to obtain information on current smoking status, habitual alcohol drinking, and use of medications. Alcohol drinkers were defined as those who drank alcohol ≥2 days per week.

Intima-media thickness of carotid arteries

The scanning procedures have been described elsewhere.[21,22] Before the study began, sonographers at all the centers received training for carotid scanning provided by the Ultrasound Research Laboratory, University of Pittsburgh. Toshiba 140A scanners equipped with a 7.5 MHz-linear-array imaging probe were used in Japan and Pittsburgh, while a Siemens Acuston Cypress scanner was used in Hawaii. The sonographers scanned the right and left common carotid arteries, the carotid bulbs, and the internal carotid arteries. For the common carotid artery segment, both near and far walls were examined 1-cm proximal to the bulb. For the bulb and internal carotid artery areas, only the far walls were examined. The scans were recorded on videotape and sent to a central laboratory for scoring. Trained readers digitized the best image for scoring and then used automated software to measure IMT over 1-cm segments of the near and far walls of the common carotid artery and the far wall of the carotid bulb and internal carotid on both sides. Measurements from each location were then averaged to determine the mean IMT. The readers were blinded to the characteristics of the participants and the study centers. The correlation coefficients of mean IMT between sonographers and between readers were 0.96 and 0.99, respectively.[24]

Coronary calcium score (CCS)

Scanning was performed at all three centers according to a standardized protocol using a GE-Imatron C150 EBT scanner (GE Medical Systems, San Francisco, CA, USA). A total of 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. These images were recorded during a maximal breath hold using ECG-guided triggering of 100-m-second exposures during the same phase of the cardiac cycle. CAC was considered to be present when three contiguous pixels (area=1 mm^2) ≥130 Hounsfield Units were observed. One trained reader at the Cardiovascular Institute, University of Pittsburgh, read the images using a Digital-Imaging-and-Communications-in-Medicine workstation and software (AccuImage Diagnostic Corporation, San Francisco, CA, USA) which calculated the coronary calcium score (CCS) by the Agatston scoring method.[25] The prevalence of CAC was defined as a CCS ≥10. We selected the cutoff point of 10 because: (1) its clinical significance,[10] (2) the possibility that scores of 0-10 could be an imaging artifact from spurious noise,[26] and (3) our intention to keep the cutoff point consistent with our previous studies.[9,22] The reader was blinded to the

characteristics of the participants and the study centers. The intra-examiner reproducibility of non-zero CCS had an intra-class correlation of 0.98.

Statistical analysis

The levels of risk factors for atherosclerosis were compared in the three populations using analysis of variance for continuous variables and the χ^2-test for proportions. Multiple linear regression analyses were used to calculate the standardized regression coefficients for the associations between inflammatory markers and IMT in each population and the total study group. The association of inflammatory markers with the prevalence of CAC in each population and the total study group was examined using multiple logistic regression models. The odds ratios and 95% confidence intervals for the prevalence of CAC with a 1-SD increment of inflammatory markers were then calculated.

In both multivariate analyses, model 2 was adjusted for age, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, fasting glucose, smoking, and alcohol consumption, while model 3 was adjusted for age and BMI. The logarithm of CRP was used in both regression models to normalize the distribution.

To examine potential confounding effects, we performed sensitivity analyses restricted to participants who were non-smokers, non-drinkers, non-hypertensives, non-diabetics, non-obese, or were not taking hyperlipidemia medications. These factors were selected because they may possibly influence the levels of inflammatory markers. A P value of <0.05 was considered significant. All the statistical tests were two-sided. IBM SPSS statistics 19 software (IBM Inc., NY, USA) was used for all statistical analyses.

Results

The baseline characteristics of the participants in the three populations are shown in Table 1. Japanese men had the highest prevalence of current cigarette smokers and alcohol drinkers among the three populations. On the other hand, Japanese men were the least obese. Japanese men also had a favorable profile with lower levels of HDL-C, inflammatory markers (CRP and fibrinogen), and atherosclerosis.

Multiple linear regression analysis showed a significant and positive association between CRP levels and mean IMT after adjustment for age in Japanese men and the total study group (Model 1 in Table 2). However, after additional adjustment for traditional risk factors or BMI, the positive associations were diminished and became non-significant (Models 2 and 3 in Table 2). Non-significant but positive trends in the American men and the total study group also disappeared after additional adjustment for traditional risk factors or BMI. Although there was a significant and positive association between fibrinogen and mean IMT in the total study group and a positive but non-significant association in the three populations after adjustment for age (Model 1 in Table 2), these associations disappeared after additional adjustment for traditional risk factors or BMI (Models 2 and 3 in Table 2). Moreover, no significant association was observed between CRP or fibrinogen levels and the prevalence of CAC (Table 3).

Spearman's rank correlation showed a positive and significant association between BMI and both CRP and fibrinogen levels in each of the three populations (*P* values all <0.05, Table 4). The sensitivity analysis restricted to participants who were non-smokers, non-drinkers, non-hypertensives, non-diabetics, non-obese, or were not taking hyperlipidemia medications showed similar results (Supplemental Tables S1 and S2). We also analyzed the association of CRP or fibrinogen with mean-IMT or the prevalence of CAC after adjustment for serum levels of n-3 polyunsaturated fatty acids. This analysis showed the results did not change materially (data not shown).

Discussion

The present study showed that the associations between inflammatory markers and subclinical atherosclerosis were not independent of traditional risk factors or BMI in three populations of men with genetically or environmentally different backgrounds. As we found that BMI was associated strongly with both CRP and fibrinogen in all three populations, the relationship of inflammatory markers with subclinical atherosclerosis may reflect the strong association between BMI and inflammatory markers.

The association between inflammation and atherosclerosis is well established. CRP also independently predicts future cardiovascular events as evidenced by its incorporation into the new clinical guidelines of the American Heart Association/American College of Cardiology.[27] However, the association of measures of subclinical atherosclerosis (i.e., CAC and IMT) with CRP or other markers of inflammation is not well established. The results of previous studies reporting the association of inflammatory markers with subclinical atherosclerosis have been controversial. Some studies showed positive associations of inflammatory markers with IMT.[11-13,28-30] However, the majority of these studies were based on univariate analysis or on analyses adjusted for age and gender without adjustment for other traditional risk factors. A few studies using multivariate analysis showed significant positive associations between inflammatory markers and IMT. For example, Wang et al. studied an offspring cohort of the Framingham Heart Study and showed a graded association between CRP and IMT independent of traditional risk factors including BMI in women but not in men.[13] Elias-Smale et al. also showed a graded association between CRP and IMT independent of traditional risk factors including BMI in elderly men and women in the Rotterdam Study.[30] To our knowledge, no previous population-based studies in middle-aged men have reported significant positive associations between inflammatory markers and IMT after adjustment for measures of obesity.

Although a smaller number of studies have examined the associations with CAC than those with IMT, the majority of these studies showed the associations between inflammatory markers and CAC were weak and the significant association, if any, disappeared after adjustment for traditional risk factors including BMI or use of medications such as estrogen or statins.[12,30,31] Only two community-based studies have shown that the inflammatory marker fibrinogen is associated positively with CAC independent of BMI.[19] However, after adjustment for all traditional risk factors including BMI, the significant association remained only in women but not in men.[19] A multi-ethnic study of atherosclerosis (MESA) showed that fibrinogen, but not CRP, was associated weakly with the prevalence of CAC, although

in participants with detectable CAC, both inflammatory markers were not associated significantly with the burden of CAC after adjustment for traditional risk factors.[20] Some studies have reported that measures of obesity are important factors among traditional risk factors for the associations observed with IMT or CCS.[16,18,31,32] However, the relationship of obesity to clinical cardiovascular disease is relatively lower than that with subclinical atherosclerosis.

In the present study, Japanese men had significantly lower levels of inflammatory markers and BMI and a significantly higher proportion of cigarette smokers compared with the other two populations. These characteristics of Japanese men were consistent with the results from previous studies.[3,33-35] In particular, CRP levels in the Japanese population have been reported to be about two to three times lower than levels measured in white Americans.[34] Similarly, plasma fibrinogen levels in Japanese subjects are lower than in Japanese-Americans.[33] Although it is known cigarette smoking is associated positively with the levels of inflammatory markers,[36,37] Japanese men with a higher proportion of cigarette smokers have lower levels of inflammatory markers. This discrepancy may be due in part to the lower prevalence of obesity in Japanese men, because there is epidemiological evidence that obesity is related positively to the levels of inflammatory markers.[33,34] There is also physiological evidence that adipocytes are a source of IL-6 and that fat stimulates monocytes and macrophages to become activated and release cytokines.[38,39]

Both CRP and fibrinogen are acute-phase proteins secreted from hepatocytes following induction of cytokines secreted by macrophages, T cells, and other immune cells.[5-7] The present study, as well as numerous other studies[11-18], demonstrated that the association of these inflammatory markers with subclinical atherosclerosis is usually weak. Although immune cells are activated in atherosclerotic lesions, the increased level of CRP or fibrinogen secreted may be very low at the early stage of atherosclerosis, whereas the increase is likely to be high at a more advanced stage of atherosclerosis. Therefore, CRP and fibrinogen may reflect the extent of atherosclerotic burden and predict cardiovascular events, although based on the findings of our study it is not clear whether CRP and fibrinogen have biological effects on atherosclerosis.

Some limitations of our study warrant consideration. The sample size was relatively small, because the study participants were limited to only men aged 40 to 49 years. Therefore, generalizability of the present findings to different age groups or women may not be possible. However, we focused on this specific gender- and age-group for important reasons, one of which was diminution of confounding by age, even if age was statistically adjusted. The other was the similarity in total cholesterol and BP levels throughout their lifetime in middle-aged Japanese and White men, unlike older age groups or women.[22,40] This characteristic allowed us to investigate the genetic effects of associations between other risk factors and atherosclerosis. The ultrasound machine used in Honolulu was different from that used in Japan and Pittsburgh. However, we evaluated the between-machine differences for mean IMT and found that this was no greater than the variation between sonographers (data not shown). We therefore consider that variations in measurement due to the machine would be relatively small, as most of the variation came from the sonographers and the readers. We accounted for reader variation by using the same reader. Because the present

study was cross-sectional, it may have underestimated the long-term effects of inflammatory markers on atherosclerosis. The present study was therefore observational and we cannot exclude the possibility of residual or unmeasured confounding factors.

The present investigation suggests that the associations between inflammatory markers and subclinical atherosclerosis may merely reflect the strong association of BMI with inflammatory markers and subclinical atherosclerosis. Further prospective studies are needed to confirm the findings of the present study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Basic characteristics of the study participants (Men aged 40-49 years, 2000-2006)

	Japanese (n = 310)	Japanese-American (n = 293)	US white (n = 297)	*P* value‡
Age (yrs)	45.1 (2.8)	46.1 (2.8)	45.0 (2.8)	<0.001
Body mass index (kg/m^2)	23.7 (3.1)	28.0 (4.6)	27.9 (4.3)	<0.001
Systolic blood pressure (mm Hg)	125.0 (16.1)	127.6 (12.6)	122.5 (11.2)	<0.001
LDL-C (mg/dL)	132.3 (36.0)	121.9 (32.8)	134.6 (33.6)	<0.001
Triglycerides (mg/dL)*	139.2 (103.3, 182.8)	150.6 (93.0, 227.0)	132.0 (92.5, 186.5)	<0.001
HDL-C (mg/dL)	54.1 (13.6)	50.7 (12.3)	47.8 (12.7)	<0.001
Fasting glucose (mg/dL)	106.9 (18.7)	112.4 (21.1)	101.8 (15.4)	<0.001
C-reactive protein (mg/L)*	0.38 (0.15, 0.67)	0.66 (0.33, 1.29)	0.96 (0.51, 1.80)	<0.001
Fibrinogen (mg/dL)	255.0 (63.6)	313.0 (65.8)	291.5 (70.1)	<0.001
Current cigarette smoker (%)	49.0	13.0	7.5	<0.001
Alcohol drinker (%)†	67.0	37.1	44.9	<0.001
Hypertension medications (%)	5.4	20.4	8.5	<0.001
Lipid-lowering medications (%)	3.5	23.1	12.5	<0.001
Diabetes medications (%)	1.9	6.7	1.0	<0.001
CCS ≥ 10 (%)	11.6	32.1	26.3	<0.001
Mean carotid IMT (mm)	0.61 (0.07)	0.73 (0.12)	0.68 (0.10)	<0.001

Values are expressed as arithmetic mean (SD) unless otherwise stated.

LDL-C, low-density lipoprotein cholesterol ; HDL-C, high-density lipoprotein cholesterol ; CCS, coronary calcium score; IMT, intima-media cthickness.

*The values of triglyceride and C-reactive protein are expressed as interquartile range.

†Alcohol drinker was defined as those who drank alcohol 2 days/week or more.

‡*P* values were calculated by analysis of variance for continuous variables or χ2-test for proportions.

Table 2

Linear regression analyses on mean carotid intima-media thickness in relation to lnCRP or fibriongen (standardized regression coefficient)

	Japanese		Japanese-American		US white		Total*	
	Coefficient	***P* value**	**Coefficient**	***P* value**	**Coefficient**	***P* value**	**Coefficient**	***P* value**
ln CRP								
Model 1†	0.14	0.01	0.08	0.20	0.11	0.06	0.10	0.002
Model 2†	0.09	0.11	−0.03	0.59	0.05	0.38	0.04	0.29
Model 3†	0.10	0.07	−0.01	0.91	0.05	0.38	0.01	0.72
Fibrinogen								
Model 1†	0.05	0.41	0.19	0.08	0.12	0.17	0.08	0.02
Model 2†	0.00	0.99	0.06	0.28	0.05	0.36	0.05	0.15
Model 3†	0.01	0.90	0.11	0.33	0.04	0.94	0.03	0.32

†Model 1 was adjusted for age. Model 2 adjusted for age, systolic blood pressure, LDL-cholesterol, HDL-choleseterol, fasting glucose, smokng, and alcohol consumption. Model 3 was adjusted for age and body mass index.

*All models were adjusted for population in addition to the total participants.

Table 3

Associations of lnCRP or fibrinogen with coronary artery calcification (coronary calcium score ≥ 10)

	Japanese	Japanse-American	US white	Total*
Odds ratio (95% CI)§ of CCS ≥ 10 for ln CRP				
Model 1†	1.29 (0.90 - 1.85)	0.94 (0.73 - 1.21)	1.17 (0.88 - 1.56)	1.09 (0.92 - 1.29)
Model 2†	1.23 (0.82 - 1.84)	0.88 (0.66 - 1.19)	0.92 (0.65 - 1.29)	0.96 (0.80 - 1.15)
Model 3†	1.10 (0.74 - 1.64)	0.84 (0.63 - 1.11)	0.86 (0.61 - 1.20)	0.90 (0.74 - 1.09)
Odds ratio (95% CI)§ of CCS ≥ 10 for fbrinogen				
Model 1†	1.29 (0.89 - 1.89)	1.08 (0.83 - 1.42)	1.27 (0.96 - 1.68)	1.21 (1.02 - 1.43)
Model 2†	1.17 (0.75 - 1.82)	1.10 (0.82 - 1.47)	1.24 (0.93 - 1.65)	1.17 (0.98 - 1.39)
Model 3†	1.20 (0.80 - 1.78)	1.04 (0.79 - 1.36)	1.12 (0.84 - 1.49)	1.11 (0.93 - 1.32)

§The odds ratios were calculated for 1SD higher of lnCRP or fibrinogen, using the logistic regression analysis. CI, confidence interval.

†Model 1 was adjusted for age. Model 2 adjusted for age, systolic blood pressure, LDL-cholesterol, HDL-choleseterol, fasting glucose, smokng, and alcohol consumption. Model 3 was adjusted for age and body mass index.

*All models were adjusted for population in addition to the total participants.

Table 4

Correlation coefficient of BMI with CRP or fibrinogen

	Japanese		Japanse-American		US white	
	r*	*p*	r*	*p*	r*	*p*
CRP	0.28	<0.001	0.43	<0.001	0.41	<0.001
Fibriongen	0.12	0.04	0.21	<0.001	0.23	<0.001

*Correlation coefficient calculated by Spearmans's rank method