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Body Mass Index and C-Reactive Protein in the Healthy Korean Aged Men

The purpose of this study was to determine the relationship between plasma C-reactive protein (CRP) and body mass index (BMI) in elderly Korean men. A review of routine health examination records were done. Out of 671 eligible elderly men, who had their routine health examination in 2001 at a Health Promotion Center of a university hospital, 367 subjects were included after excluding inflammatory conditions. Subgroup analyses were performed on those who did not smoke and exercised regularly. Body composition, blood pressure, blood samples and radiologic examinations including chest radiography and abdominal ultrasound were obtained from each subject. Age, BMI, current smoking, regular exercise, WBC count, HDL-cholesterol, gamma glutamyl transferase were independently associated with logCRP. BMI subgroups according to the Asia-Pacific guideline did not show any difference in CRP level from each other by ANCOVA (p>0.05). However, BMI groups subdivided according to our criteria showed an association with CRP; the CRP level was lowest in the group of BMI between 18.5-19.4 and showed significant difference from BMI group of the highest BMI group (≥29.0). Since elevated CRP levels are associated with higher risk for cardiovascular disease, lower BMI (18.5-19.4) levels may be advised for healthy elderly men in Korea.

Key Words : *Body Mass Index; C-reactive Protein; Aged; Korea; Men*

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INTRODUCTION

Arterial inflammation is well recognized as an essential process for atherogenesis (1). Of the markers of inflammation, with the availability of highly sensitive assay systems, C-reactive protein (CRP) levels in the low-normal range have been shown to have predictive value for subsequent clinical events among patients with cardiovascular disease (2).

Moreover, baseline levels of CRP predict the risk of future myocardial infarction, stroke, and peripheral atherosclerosis among apparently healthy middle-aged men (3) and women (4), after adjusting for other known cardiovascular risk factors. Even in the elderly, higher CRP levels were associated with cardiovascular mortality in women without cardiovascular disease (5).

In the Western countries, many studies have explored the relationship between CRP levels and determinants of cardiovascular risk factors in apparently healthy men (6-8) and women (9), and in older individuals (10). In particular, obesity is strongly associated with CRP concentration (6, 10), because adipose tissue produces proinflammatory cytokines such as interleukin-6 (IL-6), which stimulates the production of CRP (11).

In Asian populations limited studies have been conducted to determine the relationship between CRP concentration and cardiovascular risk factors. Few studies indicate that CRP levels are strongly associated with body mass index (BMI) in elderly Korean women (12), middle aged Japananese (13-15), and Asian Indian adolescents (16); however, theses studies included small numbers of elderly.

Furthermore, there has been no study which investigated whether BMI classification by WHO Asia-Pacific guideline (17) is relevant for Asian population (especially Koreans) in terms of BMI association with CRP level. Although many Korean physicians and researchers use BMI classification by WHO Asia-pacific guidelines for obesity, some researchers disagree with the classification system. Few credible published data exist in support of elevated risk of cardiovascular disease at BMI 23 to <25 in Asian population (18).

This is a cross-sectional study of Korean elderly men to determine the relationship between plasma CRP level, BMI, and other cardiovascular risk factors. We also investigated whether BMI classification by Asia-pacific guidelines for obesity is associated with CRP level.

MATERIALS AND METHODS

Subjects

Eligible study subjects were men older than 65 yr who had routine health examination at the Health Promotion Center of Asan Medical Center from May to December of 2001. Asan Medical Center is a university hospital in Seoul, Korea. The examination consisted of a medical interview, measurement of height, weight and blood pressure, collection of blood samples and radiologic examinations. During the medical interview, information on past medical history, current medication and lifestyle were obtained. All subjects wore the the same light gown for height and weight measurements. Blood samples were collected after a 12 hr fast, and they were analyzed for blood cell count, glucose, total and HDL cholesterol, triglyceride, uric acid, liver function test (gamma glutamyl transferase, alanine aminotransferase), hepatitis B surface antigen, hepatitis C antibody, rheumatoid antibody, and CRP levels. Radiologic examinations included chest radiography, ultrasonography of abdomen and upper endoscopy. Exclusion criteria included subjects with cancer, hepatitis B or C, peptic ulcer disease, pneumonia, current use of aspirin and elevated levels of white blood cell count (WBC count >10,000/μL), rheumatoid factor (RF $\geq$1:80) and CRP (CRP $\geq$1 mg/dL). Individuals with CRP level of more than 1 mg/dL were excluded to eliminate the possibility of recent infection (10). Also previous studies showed association between CRP level and risk for cardiovascular disease in healthy men and women who have CRP level $\leq$1 mg/dL (2-4). In addition, men without information on smoking status or alcohol intake were excluded.

Out of 671 eligible subjects, 367 men qualified for analyses. Permission to perform the study was obtained by the institutional review board (IRB) at Kyung-Hee Medical Center, Seoul, Korea. IRB approval from the investigator's institution includes approval to conduct a study at the health promotion center of Asan Medical Center.

Definitions

BMI was calculated as kilograms divided by the squared meters. According to the WHO Asia-Pacific guidelines for obesity (22), BMI was classified into quintiles of <18.5 kg/m^2 (underweight), 18.5-22.9 kg/m^2 (normal weight), 23.0-24.9 kg/m^2 (overweight), 25.0-29.9 kg/m^2 (obesity), and >30.0 kg/m^2 (extreme obesity). Smoking status was defined as current smoker or non-smoker (never smoked or quit smoking). Alcohol consumption was classified as current drinker (more than 1 drink a week) or non-drinker. Exercise habits were categorized as regular exerciser (more than once a week) or none. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or current use of antihypertensive medication. Fasting glucose concentration $\geq$126 mg/dL or current use of diabetes medication was a criterion for diabetes mellitus.

Assays

All the blood samples were analyzed at the clinical laboratory of the Asan Medical Center. CRP was quantitatively analyzed by a newly designed method (Immunoturbidomatic method, Integra 800, Roche, Swiss). The lower detection limit of the assay was 0.03 mg/dL, and the coefficient of variation was 1.5-1.8% within group, an 2.7-2.9% between groups.

Statistical analysis

Differences in proportions and means of variates across the groups were assessed by use of chi-square test and ANOVA, respectively. Since the distribution of CRP levels was highly skewed to the right, CRP values were log-transformed for multivariate linear regression analysis. Analysis of covariance was used to compare log CRP levels adjusting for compounding variables across BMI categories, under a general linear model. The geometric mean values of the CRP were presented in the box plot, for ease of interpretation.

All analysis were performed using SPSS 10.0 for Windows, and statistical significance was defined as $p<0.05$.

RESULTS

The median age of the study subjects was 68.0 yr (interquartile range=66.0-71.0), and the median CRP value was 0.10 (interquartile range=0.07-0.19). Current smokers were more common in the underweight group, and the prevalence of hypertension and diabetes increased with higher BMI levels. Triglyceride concentration and alanine aminotransferase (ALT) level were also increased in overweight, obesity, and excessive obesity category.

Table 1. Simple linear regression anaylsis for $\log_{10}$CRP in the 367 subjects

Variable	Regression coefficient	*p* value
Age (yr)	0.009	0.048
Body mass index	0.016	0.010
Hemoglobin (g/dL)	0.029	0.086
WBC count ($\times 10^3/\mu$L)	0.068	<0.001
Uric acid (mg/dL)	0.031	0.023
Total cholesterol (mg/dL)	0.000	0.724
Triglyceride (mg/dL)	0.000	0.093
HDL-cholesterol (mg/dL)	-0.005	0.001
ALT (U/L)	0.003	0.012
GGT (U/L)	0.000	0.001
Creatinine (mg/dL)	0.156	0.141

HDL, high density lipoprotein; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase.

Table 2. Multivariate backward linear regression model predicting log_{10}CRP in the 367 subjects*

Variable	Regression coefficient	*p* value
Age (yr)	0.012	0.006
Body Mass Index (kg/m^2)	0.014	0.021
Regular exercise†	-0.085	0.016
Current smoking‡	0.128	0.002
WBC count ($\times 10^3/\mu$L)	0.043	0.001
HDL-cholesterol (mg/dL)	-0.005	0.002
GGT (U/L)	0.002	<0.001
Triglyceride (mg/dL)	0.000	0.097

R^2 (coefficient of determination) is 0.185.
*Alanine aminotransferase, hemoglobin, uric acid were excluded in the final model. †Regular exercise was entered in the model as 1; no regular exercise, 2; regular exercise (more than once a week). ‡Current smoking was entered in the model as 1; no current smoking , 2; current smoking. HDL, high density lipoprotein; GGT, gamma glutamyl transferase.

As expected, univariate correlation analyses of factors relating to logCRP level showed the highest correlation with white blood cell count (Table 1). HDL-cholesterol, gamma glutamyl transferase (GGT), age and BMI also had significant correlation with log CRP level (Table 1).

In stepwise multiple linear regression analysis, age, BMI, current smoking, regular exercise, WBC count, HDL-cholesterol, GGT remained as factors independently associated with log CRP. Alcohol drinking, hypertension, diabetes mellitus, past history of stroke, past history of myocardial infarction, hemoglobin, uric acid, triglyceride, ALT were not independently significant factors. This model explained 17.9% of variance in log CRP levels (Table 2).

Subgroup analyses

Subgroup analyses were performed on those who did not smoke and who exercised regularly. This was performed because smoking and exercise were significant confounding factors with log CRP in multivariate analysis. Out of 367 men, 167 non-smoker who exercised regularly (more than once a week) were included. For this analysis, we subdivided BMI into 5 categories: <18.5, 18.5 to 19.4, 19.5 to 24.9, 25.0 to 28.9, and ≥29.0. The category was made after dividing BMI by 0.5 and then merging the combining adjacent BMI categories which showed no apparent difference in CRP levels.

When we analyzed for association between CRP levels and our new BMI subgroups by ANCOVA, the highest BMI group (BMI ≥29.0) showed significant difference in CRP concentrations from BMI group of 18.5-19.4 (p=0.038) (Fig. 1). There was a trend towards difference in CRP levels between the BMI of 25.0-28.9 and BMI of 18.5-19.4 (p=0.105). Similar analysis was conducted between CRP concentrations and BMI subgroups according to the WHO guidelines. The Asia-Pacific guideline BMI subgroup did not show any difference in CRP concentrations from each other after adjusting for covariates by ANCOVA (p>0.05).

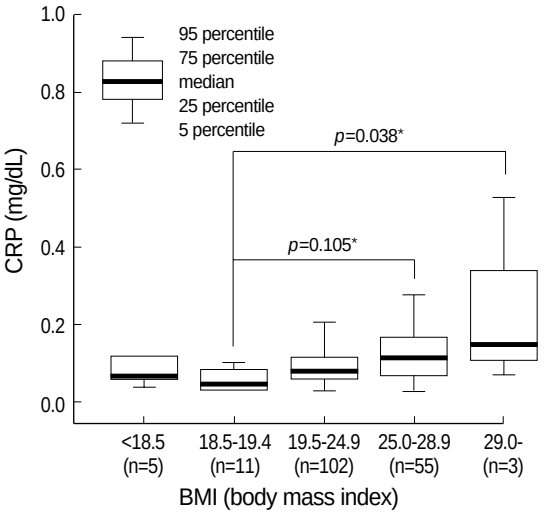

Fig. 1. Box plot of CRP concentrations for nonsmoking elderly men who exercise regularly, according to new BMI classification.
*p values were calculated by ANCOVA for log CRP after adjusting the covariates of age, hemoglobin, WBC count, uric acid, triglyceride, HDL-cholesterol, AST, GGT, alcohol drinking, history of stroke, myocardial infarction, diabetes, hypertension.

DISCUSSION

This study examined the relationship between plasma CRP concentrations and BMI in the old Korean men. We showed that among healthy elderly men, BMI was positively associated with CRP concentrations. Similar to previous reports (6, 8, 10, 15), age, exercise level, smoking status, WBC count, HDL-cholesterol, and GGT were independently associated with CRP concentrations. There was no significant difference in CRP level between normal (BMI 18.5-22.9), overweight (BMI 23.0-24.9), or obesity subgroup (BMI 25.0-29.9) among nonsmoker who exercise regularly according to the BMI category of WHO Asia-Pacific guideline. However, when we classified the BMI differently (lower than 18.5, 18.5 to 19.4, 19.5 to 24.9, 25.0 to 28.9, 29.0 or higher), CRP concentrations showed a J shape association with BMI subgroups. CRP concentration was the lowest in BMI of 18.5-19.4, and therefore, we propose that BMI of 18.5-19.4 would be ideal for Korean older men to reduce their risk for cardiovascular disease. In the United States, an association between BMI and death from cardiovascular disease also showed a J-shaped pattern (20), and the lowest risk of death from cardiovascular disease was BMI of 20.5-24.9.

IL-6 or TNF-α levels may be a better predictor of cardiovascular events than CRP concentrations in old adults (21, 22). However, plasma IL-6 concentrations has a circadian variation. In another report, CRP concentrations rather than IL-6 was a marker which independently predicted cardiovascu-

lar disease (23). Therefore, CRP concentration provides a reliable, and feasible index of inflammation and cardiovascular risk compared to other inflammatory markers (15).

The correlations between CRP and BMI in this study were lower than that found in old individuals of Western countries (10). The possible explanation may be that our study did not include women, who usually have higher correlation between BMI and CRP levels (24). Also Asian people usually have higher proportion of body fat compared to Western people with the same BMI (24). The correlations between CRP and BMI appeared to be lower than that found in a report of middle-aged Korean adults (25). As people age, there is a gradual increase of adipose tissue in the abdomen (visceral depots) and decrease in subcutaneous fat (26). Fat-free mass is also reduced with age.

Stevens et al. (27) suggested that although greater BMI was associated with higher mortality from cardiovascular disease in men and women up to 75 yr of age, the relative risk declined with age. Furthermore, after 75 yr of age, the risk for cardiovascular disease did not increase significantly with higher BMI. Other investigators have indicated a risk for cardiovascular disease to be less in Asian people with a BMI of $\leq$ 25 (28).

Possible limitations of this study include the cross-sectional design, which can not account for acute weight change. The sample size for the excessive obesity was small, however, this was not unexpected. According to the 1998 Korea National Health and Nutrition Survey, the percentage of extreme obesity (BMI $\geq$30) among Korean men $\geq$70 yr old was 0% (29).

Highly sensitive CRP levels increased with acute infection and trauma. Thus testing should be avoided within 2 to 3-weeks after an upper respiratory infection. Although we did not exclude people with history of upper respiratory infection 2-3 weeks ago, we excluded acute infection based upon abnormal chest radiography, WBC >10,000/μL, and CRP >1 mg/dL. Despite these efforts, we still may have missed subjects with underlying infection. Another limitation of this study is the lack of generalizability. This study result is applicable to healthy Korean old men living in Korea, and it may not apply to individuals who have comorbid disease or who live in other countries.

In conclusion, our study showed that lower category of BMI (18.5-19.4) than WHO Asia-Pacific guideline for normal weight (BMI 18.5-22.9) had the lowest levels of CRP for nonsmoking elderly men who exercise regularly. Since high levels of CRP are associated with increased risk for cardiovascular disease, low BMI (18.5-19.4) levels may be advised for healthy old men in Korea.

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