Original Article

The association of plasma C-reactive protein levels with anthropometric and lipid parameters in elderly Taiwanese

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C-reactive protein (CRP), a plasma inflammation marker, has been known to play a role in the development of cardiovascular diseases. This study aims to evaluate the association of CRP with anthropometric and plasma lipid parameters in elderly Taiwanese 65 years or older. Data from the Elderly Nutrition and Health Survey in Taiwan (1999-2000), a national probability sampling study conducted to gain an understanding of the dietary pattern, and nutritional and health status of elderly Taiwanese were analyzed. Results showed that in men, CRP was positively correlated with age and waist-to-hip ratio (WHR) (both $p<0.05$) whereas in women, CRP was positively correlated with waist and WHR but negatively correlated with HDL-C (all $p<0.05$). Linear regression analysis showed that log CRP was positively associated with WHR in both genders ($p<0.05$) after adjusting for confounders. The correlation of CRP with WHR was stronger than that with both waist circumference and body mass index (BMI). Log CRP was inversely associated with HDL-C in women, but not men. The study suggests that among the anthropometric parameters examined, WHR is a stronger predictor for elevated CRP in elderly Taiwanese men and women. Whereas low HDL-C is a predictor among the plasma lipid parameters for elevated plasma CRP, at least in women. Gender differences exist in the association of CRP with anthropometric and lipid parameters.

Key Words: C-reactive protein, elderly, waist-to-hip ratio, high-density lipoprotein-cholesterol, anthropometric indices

INTRODUCTION

Inflammation has been shown to play a role in the development of atherosclerosis.[1,2] C-reactive protein (CRP), one of the most extensively studied plasma inflammatory marker, has been recognized as a strong predictor for cardiovascular disease.[3-5] Plasma concentration of CRP is usually low or even undetectable in healthy subjects. However, it can increase up to 100 times or more during the acute phase of inflammation. It is important to understand the potential risk factors underlying the elevated CRP levels in healthy subjects.

Many studies conducted in Western countries have explored the relationship between CRP and related cardiovascular risk factors in healthy men and women,[6-8] and in older persons.[9,10] Raised plasma CRP concentrations have been shown to be associated with aging, smoking, elevated plasma triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C) levels, obesity and chronic infections.[7,11] However, ethnicity and gender have also been reported to play a role.[12-15] Lear et al.[12] observed that CRP levels were significantly lower in individuals of Chinese descents compared to European descents in Canada, but the differences disappeared after correcting for either body mass index (BMI) or waist. Albert et al.[13] reported that Asians, especially East Asians, residing in North America had lower CRP levels compared to other races/ethnicities in the same continent. In the Multiethnic Study of Atherosclerosis (MESA) cohort study, Lakoski et al.[14] observed that women had higher CRP levels than men in all ethnic groups examined including Caucasians, Chinese, African American and Hispanics. Visser et al.[15] observed a greater proportion of women than men with elevated CRP levels when stratified by BMI. However, to date, few studies have examined the association of plasma CRP concentration with anthropometric body fatness indicators and plasma lipid parameters in older adults in Asian populations. This study aims to examine these associations in a Taiwanese population of 65 years or older.

METHODS

Subjects and design

Data from the Elderly Nutrition and Health Survey in Taiwan (1999-2000) (Elderly NAHSIT) that was conducted to assess the status of diet, nutrition and health of

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a national representative sample of persons 65 years or older in Taiwan were analyzed. The study design and methods of the survey have been described by Pan et al.[16] Briefly, the survey employed a stratified, clustered, and multi-staged probability sampling design. Three hundred and fifty nine townships and villages in Taiwan were divided into 13 strata according to the degree of urbanization and geographic characteristics. A total of 39 township and 78 villages were chosen for the survey using the probability-proportional-to-population-size method. All Taiwanese civilian citizens 65 years or older residing in Taiwan on January 1, 1999 were eligible for this study. Those residing in military institutions, hospitals, nursing home or other institutions during the period of recruitment were excluded. A total of 2028 persons with equal number of men and women were recruited to participate in the study. The survey was approved by the reviewers appointed by the Department of Health. All participants signed consent forms.

Data collection

The study included two components: an in-house in-person questionnaire interview and a physical examination. The questionnaire included questions to elicit information on demographic, dietary intake and lifestyle parameters. Physical examination included measurements of anthropometric parameters, blood pressure, and blood and urinary biomarkers.

Anthropometric measurements included height, weight, waist circumference, hip circumference, and skinfold thickness. Height and weight were measured using the German SECA 707 continuous display electronic scale. Subjects were asked to remove their shoes and outdoor clothes. Height was measured to the closest millimeter and weight to the closest 0.1 kilogram. BMI was calculated as weight in kilogram divided by the square of height in meters (kg/m^2). Waist circumference was measured horizontally at the level of the participant's natural waist, which was identified as the level at the hollow molding of trunk when the trunk was concaved laterally. Hip circumference was measured horizontally at the level of the greater trochanters. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

At local work-stations, each subject was sampled for a fasting blood specimen containing sodium fluoride and heparin for analysis of whole blood glucose and another containing ethylenediaminetetraacetic acid (EDTA), as an anticoagulant, for measurements of all other plasma parameters. The EDTA-containing blood was centrifuged to separate plasma which was aliquoted, frozen in a liquid nitrogen tank and then delivered to the Academia Sinica for storage at -70°C until time of analysis. Frozen plasma samples were then used for analyses of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), TG, LDL-C and CRP in project-approved clinical laboratories. Further detail on the analysis of blood samples is available elsewhere.[16-18]

Data analysis

Participants' descriptive data were weighted according to sampling design[16] and the t-test was performed to compare the means of age, anthropometric measurements and serum parameters stratified by gender. Pearson's correlation analysis was used to assess the crude associations of CRP with each of the anthropometric measurements and lipid parameters stratified by gender. CRP values which are known to be skewed were transformed logarithmically for linear regression analysis. Multivariate linear regression analyses were performed to evaluate the associations of log CRP with age, individual anthropometric variables and lipid parameters adjusted for confounding factors. Since BMI, waist circumference, and WHR were highly inter-correlated, only one of the three anthropometric indices was introduced into the linear regression model each time in order to avoid the collinearities. Similarly,

Table 1. Characteristics of study subjects[†]

Variables	Men			Women		
	N	Mean	Standard error	N	Mean	Standard error
Age, y	709	72.76	0.35	642	72.80	0.42
Weight, kg	702	62.17	0.43	635	54.39	0.60***
Height, cm	702	163.08	0.22	635	150.26	0.35***
Waist, cm	701	85.52	0.32	633	81.68	0.62***
BMI, kg/m^2	702	23.14	0.15	634	23.86	0.24**
Plasma lipids						
Total chol., mg/dL	692	196.56	2.15	635	213.17	2.03***
LDL-C, mg/dL	687	120.95	1.83	634	128.06	2.01**
HDL-C, mg/dL	693	51.84	0.68	637	57.07	0.96***
TG, mg/dL	693	115.13	2.79	637	139.38	4.27***
SBP, mmHg	705	133.95	1.28	638	139.69	1.04***
DBP, mmHg	705	76.54	0.59	638	75.49	0.64
FBG, mg/dL	693	112.32	1.68	635	115.86	2.40
CRP, mg/dL	683	0.47	0.06	682	0.47	0.04
CRP, mg/dL[‡]	635	0.25	0.01	573	0.27	0.01

Chol = cholesterol, LDL-C = low-density lipoprotein-cholesterol, HDL-C = high-density lipoprotein-cholesterol, TG = triglyceride, SBP = systolic blood pressure, DBP = diastolic blood pressure, FBG = fasting blood glucose.

[†]All values were weighted using SUDAAN, not including aboriginal Taiwanese.

[‡]Not including aboriginal Taiwanese and those whose CRP >1 mg/dL.

** p<0.01 and *** p<0.001, indicating significantly different from the men on basis of t-test.

since TG was highly correlated with LDL-C, only LDL-C and HDL-C were included in the linear regression model 2A, B and C. The regression models tried to reduce the collinear effects to the minimum. Data from aboriginal Taiwanese individual were excluded from analyses because of the limited sample size. Our correlation analysis and linear regression analysis also excluded CRP values >1 mg/dL. CRP values >1 mg/dL are indicative of clinical inflammation. During the acute phase of inflammation, CRP values can be hundreds times higher than normal values and that can greatly skew the average or interfere with the analysis.[14,19,20] Thus, those extreme values are inappropriate for inference of general elderly population. Of the 1352 non-aboriginal study subjects, 104 (7.7%) had CRP >1 mg/dL and were excluded from the analysis. The statistical software package SAS (SAS Institute Inc, Cary, NC, USA) version 9.1 was used for all statistical analyses and SAS-callable SUDAAN software (Research Triangle Institute, Research Triangle Park, NC) version 10.0 was used for weighted descriptive data according sampling design. A $p<0.05$ was set as the level of statistical significance. Probability levels of $p<0.01$ and $p<0.001$ were also indicated.

RESULTS

Table 1 shows the characteristics of participating subjects. The average age was 73 years. Women had higher BMI, plasma concentrations of total cholesterol, LDL-C, HDL-C, and TG, and systolic blood pressure (SBP) than men ($p<0.05$).

Table 2 shows Pearson correlations of CRP with age, anthropometric indices, and lipid parameters stratified by gender. For men, CRP were positively correlated with age and WHR (coefficient = 0.089 for age; coefficient = 0.122 for WHR, both $p<0.05$) and marginally negatively correlated with HDL-C (coefficient = -0.07, $p<0.1$). For women, CRP were positively correlated with BMI, waist, and WHR (coefficient = 0.07, $p<0.1$ for BMI; coefficient = 0.108, $p<0.05$ for waist; coefficient = 0.120, $p<0.05$ for WHR) and negatively correlated with HDL-C (coefficient = -0.124, $p<0.05$).

Table 2. Pearson's correlation analysis of CRP† with age, anthropometric indices and plasma lipid levels stratified by gender in elderly Taiwanese.

Variables	Men		Women	
	N	Coefficient	N	Coefficient
Age	656	0.089*	592	0.006
BMI	651	-0.003	586	0.070‡
Waist	652	0.024	586	0.108*
Waist-to-hip ratio	650	0.122**	584	0.120**
Total cholesterol	655	0.052	590	-0.027
LDL-C	650	0.053	589	-0.008
HDL-C	656	-0.070‡	592	-0.124**
TG	656	0.058	592	0.066

LDL-C = low-density lipoprotein-cholesterol, HDL-C = high-density lipoprotein-cholesterol, TG = triglyceride.
†Not including aboriginal Taiwanese and those whose CRP >1 mg/dL
‡0.5<p<0.1
* $p<0.05$ and ** $p<0.01$, indicating significant correlation coefficient within gender.

Table 3. Linear regression analyses of the associations† of log CRP with age, anthropometric measurements and plasma lipid levels in elderly Taiwanese‡.

Variables	Log CRP (men)		Log CRP (women)	
	regression coefficient	t	regression coefficient	t
Model 1				
Age	0.0152	2.46*	-0.0060	-0.90
LDL-C	0.0014	1.42	-0.0002	-0.19
HDL-C	-0.0019	-0.81	-0.0054	-2.10*
TG	0.0008	1.66	0.0002	0.58
Model 2A				
Age	0.0131	2.11*	-0.0038	-0.55
BMI	-0.0027	-0.25	0.0113	1.16
LDL-C	0.0014	1.46	-0.0002	-0.15
HDL-C	-0.0034	-1.51	-0.0054	-2.24*
Model 2B				
Age	0.0138	2.24*	-0.0063	-0.95
Waist	-0.0011	-0.30	0.0063	1.71§
LDL-C	0.0015	1.47	-0.0002	-0.20
HDL-C	-0.0035	-1.57	-0.0046	-1.88§
Model 2C				
Age	0.0144	2.36*	-0.0082	-1.22
Waist-to-hip ratio	1.4959	2.67*	1.1940	2.34*
LDL-C	0.0011	1.15	-0.0002	-0.23
HDL-C	-0.0018	-0.81	-0.0043	-1.79§

LDL-C = low-density lipoprotein-cholesterol, HDL-C = high-density lipoprotein-cholesterol, TG = triglyceride.
†All models adjusted for smoking, alcohol drinking and physical activity.
‡Not including aboriginal Taiwanese and those whose CRP > 1 mg/dL
§0.5<p<0.1
* $p<0.05$ and ** $p<0.01$.

Table 3 shows the multivariate linear regression analyses of the associations of log CRP with age, lipid parameters and anthropometric measurements. In model 1, log CRP was positively associated with age in men (β = 0.0152, $p<0.05$) and negatively associated with HDL-C in women (β = -0.0054, $p<0.05$), adjusted for smoking, alcohol drinking, and physical activity. In model 2A, log CRP was positively associated with age in men (β = 0.0131, $p<0.05$) and negatively associated with HDL-C in women (β = -0.0054, $p<0.05$). In model 2B, log CRP was positively associated with age in men (β = 0.0138, $p<0.05$) and were marginally associated with waist and HDL-C in women (β = 0.0063 for waist; β = -0.0046 for HDL-C, both $p<0.1$). In model 2C, log CRP was positively associated with age and WHR in men (β = 0.0144 for age; β = 1.4959 for WHR, both $p<0.05$) and also positively associated with WHR in women (β = 1.1940, $p<0.05$). Log CRP was marginally negatively associated with HDL-C in women (β = -0.0043, $p<0.1$). Models 2A, B and C were also adjusted for smoking, alcohol drinking and physical activity.

DISCUSSION

Body fatness indicators

Results of the present study suggest WHR is a better body fatness indicator than waist or BMI in reflecting the elevated plasma CRP in elderly Taiwanese. Waist circumference shows marginal association and only in women. Plasma CRP has been observed to be strongly associated with visceral obesity as indicated by greater waist circumference and WHR compared to other parameters of obesity, such as BMI, in healthy Japanese.[21] On the other hand, Lear et al[12] reported that BMI and waist circumference were strongly correlated with CRP levels in healthy women of Chinese and European descents 18 years or older in Canada, and WHR was only weakly correlated with CRP in both genders. Rexrode et al.[22] reported that age-adjusted CRP levels had stronger correlations with BMI and waist circumference, compared to WHR in women 45 years or older in US. Taken together, none of these anthropometric fatness indicators is consistently superior to others in predicting plasma CRP levels, but WHR and waist circumference, indicators of visceral obesity, appear to correlate better with plasma CRP levels compared to BMI for Asians. Compared to BMI, waist circumference and especially WHR are better indicators of central obesity and it is known that central obesity is a predominant type of obesity in Asians.[23-25]

The present study also shows that there are gender differences in the association between CRP and anthropometric indices. Plasma CRP correlates better with anthropometric indicators in women than in men. Gender differences in the association between plasma CRP and anthropometric indicators have been observed by others. Nakanishi et al.[19] observed that obesity status was associated with increased levels of CRP in both sexes. However, obese women had much higher levels of CRP than did non-obese women. Arena et al.[26] observed significant associations between CRP and traditional cardiovascular risk factors, such as BMI in female subjects, but not in male subjects. The possible explanation for these gender differences may be related to the differences in the percentage of body fat and body fat distribution between the two genders. At a similar BMI, women have a higher percentage of body fat than men.[27] Adipose tissue secrets pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, that exert major control on the synthesis of CRP.[28-30]

Plasma lipid parameters

The present study shows that among the lipid parameters examined, plasma HDL-C shows the strongest association with plasma CRP levels while LDL-C and TG are not significantly associated with CRP in either gender. These findings are line with the observation of Albert et al.[31] In their multi-center and community-based study, CRP levels were significantly correlated with HDL-C scores ($r = 0.13$ in men, $r = 0.24$ in women), but not with total cholesterol and LDL-C scores as determined by the Framingham coronary heart disease risk score in middle-aged men and women without hormone replacement therapy. Similar findings were observed in the US Women's Health Study, in which Bermudez et al.[32] reported that after adjusting for confounders, CRP was significantly associated with HDL-C in women (β coefficient = -0.01), but not with total cholesterol. On the other hand, Lim et al.[20] observed that the CRP level was significantly correlated with TG ($r = 0.14$) and HDL-C ($r = -0.1$) in Koreans aged 40-69 years whereas Yen et al.[33] observed a significant positive correlation of CRP with TG (β coefficient = 0.00188) and a negative correlation of CRP with HDL-C/LDL-C ratio (β coefficient = -0.90270) in 20-80 year-old healthy Chinese men who participated in voluntary health examinations at a metropolitan university hospital center during 1997 to 2002 in Taiwan. Taken together, the association of CRP with lipid parameters is not clear at the present time. Among plasma lipid parameters examined, none of these lipid parameters predicts elevated CRP in elderly men and women with consistently. However, CRP appears to have a stronger negative correlation with increasing HDL-C than with other lipid parameters examined, especially in women. In the present study, the strength of the correlation between CRP and HDL-C even in women is weaker than those observed in Western populations. In the study of Albert et al.,[31] the correlation coefficient was 0.24 in women, whereas in the study of Bermudez et al.,[32] it was -0.01. Both values are greater than the values observed in the present study. Thus, it appears that there are some general differences between the Eastern and Western populations with regard to the association between plasma CRP and plasma lipid levels. However, the significances of these differences remain to be determined.

Age

Results of the present study show that age is positively associated with CRP in elderly Taiwanese men, but not in women. Increasing age has been observed to be positively associated with raised CRP in some earlier studies.[20,31,32] In the US Women's Health Study, Bermudez et al.[32] observed that CRP was significantly associated with age. Albert et al.[31] observed that CRP was significantly correlated with age in men, but not in women, regardless of hormone therapy use. Lim et al.[20] observed that CRP was significantly correlated with age in Korean men and women aged 40-69 years. Aging was associated with increasing inflammatory activity in the blood, including increased circulation levels of TNF-α,[34] an early mediator of the acute-phase response. It leads to the production and release of chemokines, interleukin-6, and CRP.[35] Increased inflammatory activity in the elderly may reflect age-related pathological processes. The reason why the association between CRP and age only exists in Taiwanese elderly men, but not in women is not clear. Since all subjects in the present study were 65 years or older, the effect of age can not be shown.

Conclusion

The present study shows that among the anthropometric parameters examined, WHR is a better predictor for elevated CRP concentrations in elderly Taiwanese men and women. The association between CRP and WHR is stronger than that of CRP with waist circumference or BMI. Among the plasma lipid parameters examined, low HDL-C can predict elevated plasma CRP in women. Gender differences exist in the association of CRP with anthropometric and lipid parameters. Further studies are needed to investigate the factors that impact plasma CRP levels.

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AUTHOR DISCLOSURES

Author's declaration of Conflict of Interest was addressed in the acknowledgment. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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Original Article

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台灣老人血漿 C-反應蛋白與體位及血脂指標的關聯

C-反應蛋白(C-reactive protein, CRP)是一已知的發炎指標，在心血管疾病的發展上扮演重要的角色。本研究的目的在探討此 C-反應蛋白與體脂肪和各種血脂蛋白的關係。本研究分析老人營養健康狀況調查 1999-2000 台灣地區 65 歲以上老人之資料。結果顯示對男性而言，C-反應蛋白與年齡和腰臀圍比(waist-hip ratio)呈正相關(p<0.05)；對女性，C-反應蛋白則與腰圍、腰臀圍比呈正相關，但與高密度脂蛋白(HDL-C)呈負相關(p<0.05)。多變項線性迴歸分析，在控制干擾因子條件後，發現無論男或女性腰臀圍比越高，則 log C-反應蛋白越高(p<0.05)。且腰臀圍比對 log C-反應蛋白的相關性強度大於腰圍和身體質量指數(BMI)。而在老年女性中，高密度脂蛋白越高，則 log C-反應蛋白越低。因此在各種肥胖指標中，無論是台灣老年男性或女性，腰臀圍比是一個預測 C-反應蛋白較好的指標。而在血脂蛋白指標中，對老年女性而言，高密度脂蛋白則是一個預測 C-反應蛋白較好的指標。C-反應蛋白與體脂肪和血脂蛋白指標間具有性別差異。

關鍵字：C-反應蛋白，老年人，腰臀圍比，高密度脂蛋白膽固醇，體位指標