Epidemiology

Association of C-reactive Protein, Smoking and Metabolic Syndrome Among the Health Check-up Population

Kuo-Liong Chien,[1,2] Hsiu-Ching Hsu,[2] Ming-Fong Chen[2] and Yuan-Teh Lee[2]

Background: C-reactive protein (CRP) is considered a global inflammatory burden indicator. It was unknown which metabolic syndrome risk factor components could predict CRP levels and possible interaction with smoking in healthy young and elderly Taiwanese.

Materials & Methods: We collected totally 6,406 adult subjects (41.4% women) from January to December 2001 from the health screening program in a tertiary hospital in Taiwan. High CRP was classified as more than 5.31 mg/L, which was the 90th percentile cutoff value. Components of metabolic syndrome were defined by the modified Adult Treatment Panel III criteria.

Results: There were 13.5% of the study population with age older than 65 years, with 7.2% abstinence and 17.3% current smokers. The average CRP levels, after adjusting for gender and smoking effects, were 3.43 mg/L in young and 4.64 mg/L in elderly population ($p < 0.0001$). The prevalence rate of metabolic syndrome was 19.4%, higher in elderly than young age (29.1% *vs*. 17.9%, $p < 0.0001$). CRP levels were positively related with smoking status. After adjusting for multiple variables such as gender and smoking status, high CRP levels still strongly associated with metabolic syndrome.

Conclusions: CRP was significantly associated with smoking and metabolic syndrome. Inflammation, smoking and atherosclerotic risks were interrelated among healthy population in Taiwan.

Key Words: C-reactive protein • Smoking • Metabolic syndrome • Health check-up

INTRODUCTION

Inflammation is an important component in atherosclerosis, and arterial wall responds to injury induced by cardiovascular risk factors such as smoking, elevated cholesterol and hyperglycemia.[1] C-reactive protein (CRP) is considered to be a global inflammatory burden indicator, and high CRP is an indicator for further cardiovascular events.[2] The CRP level could predict outcome in patients of acute coronary syndrome, even at low cholesterol levels.[3] Recent data demonstrated increased CRP predicted future cardiovascular events in various populations, such as healthy men and women.[4] CRP is useful to identify individuals eligible for risk factor modification who otherwise would be ignored.

Metabolic syndrome, including high blood pressure, glucose, triglyceride level, low high-density lipoprotein cholesterol and obesity, is characterized with multiple risk clustering and as early atherosclerosis risk due to metabolic derangement. Metabolic syndrome, clustering of atherosclerotic risk factors, is common among various populations,[5] and has great impact on cardiovascular diseases. It is strongly related to smoking and physical

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inactivity.[6] Furthermore, smoking can stimulate the process of inflammation, and worsen the severity of atherosclerosis. Tobacco smoking elicits many health injuries and becomes a public health problem in the non-western countries. It stimulates the inflammatory response and is associated with various atherosclerotic risk factors in general population. Among low coronary heart disease but high stroke rate countries such as Asian-Pacific countries,[7-9] the prevalence rates of smoking and metabolic syndrome increased greatly in recent years due to urbanization and globalization. It is important to understand the relationship of CRP and metabolic syndrome and possible interaction of smoking on atherosclerotic risk among Taiwanese population.

In this study, we reported the distributions of CRP and metabolic syndrome among the health check-up population and investigated the associations of CRP, metabolic syndrome, and smoking status. Also, we stratified the participants to explore whether differences existed between young and elderly populations.

METHODS

Study design and subjects

We collected a total of 6,406 adult subjects (41.4% women) from January to December 2001 from the health screening program in a tertiary hospital in Taiwan. The protocol was approved by the IRB of National Taiwan University Hospital. All participants were enrolled voluntarily. Details of subjects' medical histories such as medications, hospitalization and smoking status were asked in the structural questionnaires. Standardized procedures of physical examination, such as anthropometric measures and blood pressure, were performed.[10,11] Blood pressure was measured in the rest position by trained medical assistants. Body mass index (BMI) was calculated as weight (in kilograms)/square of height (in meters).

Blood sampling and analytic methods

The procedures of blood sampling and analytic methods were described in a previous paper.[12] In brief, blood sample was collected from each participant after they had fasting status at least 12 hours. Serum total cholesterol levels were measured using the CHOD-PAP method (Boehringer Mannheim, Germany). HDL-C was measured following precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid and magnesium ions (Boehringer Mannheim, Germany).[13] Triglyceride concentrations were measured by the GPO-DAOS method (Wako Co., Japan). All of the lipids mentioned above were measured using a Hitachi 7450 automated analyzer (Hitachi, Japan). LDL-C concentrations were calculated using the Friedewald formula.[14] CRP was measured by automated nephelometric immunoassay using a Beckman Array instrument (Beckman Array 360 system, Canada). All the measures of both samples were carried out in the single hospital. The coefficient of variation was 5%.

Definition of binary variables and metabolic syndrome

High CRP was classified as more than 5.31 mg/L, which was the 90th percentile cutoff value among the study population. Smoking status was stratified into never, abstinence and current categories. The metabolic syndrome status was defined by criteria as defined in the Third Adult Treatment Panel of the National Cholesterol Education Program,[15] modified to use BMI data instead of waist circumference cut-off points. Therefore, any three of following criteria defined as following: 1) blood pressure of at least 130/85 mmHg or treated hypertension; 2) serum triglyceride of at least 150 mg/dL; 3) HDL cholesterol of < 40 mg/dL in men and < 50 mg/dL in women; 4) fasting glucose of 110 mg/dL or more; 5) BMI of 27 kg/m2 or greater, which was modified from WHO expert committee.[16]

Statistical analysis

We described the prevalence of metabolic syndrome status and components in gender and age-specific groups. The age-standardized prevalence rates of the metabolic syndrome were calculated by direct standardization of world and European populations. CRP levels were plotted by box plot of the median, and interquartile ranges were presented due to non-normal and left-skewed distribution of CRP levels. We tested the differences of CRP distribution among groups by nonparametric methods, such as the Wilcox rank sum test and Kruskal-Wallis test and checked the associations between continuous variables by Spearman correlation coefficients. We presented contingency tables for metabolic syndrome and high CRP status and used the chi-square test and logistic regression

for inference and estimation of parameters.

The effects of metabolic syndrome on CRP levels were stratified and tested by logistic regression models, adjusting for age and smoking status. We calculated how closely predicted outcomes agreed with actual outcomes by calibration ability by testing the Hosmer-Lemeshow chi-square statistic,[17] dividing the population risk for high CRP status, and we plotted figures to compare the difference between predicted and observed prevalence and checked the goodness of fit test statistics. Small chi-square test statistics indicated good calibration, and values exceeding 20 indicated significant lack of calibration. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC) and STATA version 9 (Stata Corp., College Station, Texas).

RESULTS

The prevalence distribution of metabolic syndrome in age-specific groups had crossover trends (Figure 1). Women's rates increased progressively as age increased, and men's rates plateaued beginning at 45 years old. Women had lower rates than men before 55-64 years old, and had higher metabolic syndrome after 65 years old; both reached peak in the eldest age group. Table 1 shows the distribution of atherosclerotic risk factors among the study population. Women had lower systolic and diastolic blood pressure, body mass index, triglyceride, LDL cholesterol, fasting glucose, daily smoking amount, and WBC counts, and had higher HDL cholesterol levels than men. The CRP concentrations and age were not significantly different between genders (Table 1). For binary measures of various risk factors, women had higher prevalence of hypercholesterolemia high BMI, and lower rates of high LDL, hypertriglyceridemia and current smoking rates. Women had lower metabolic syndrome rate than men (14.9% in women *vs*. 22.6% in men, $p < .0001$) (Table 2).

Table 3 shows the CRP distributions of median and inter-quartile ranges between each atherosclerotic risk factor or not. We found the median, 25th and 75th percentile values of CRP were persistently higher in risk factor group than the counterpart, indicating CRP concentrations were strongly associated with various atherosclerotic risk factors, especially the highest CRP values in obesity and hyperglycemia status.

The average CRP levels, after adjusting for gender and smoking effects, were 0.343 mg/dL in young and

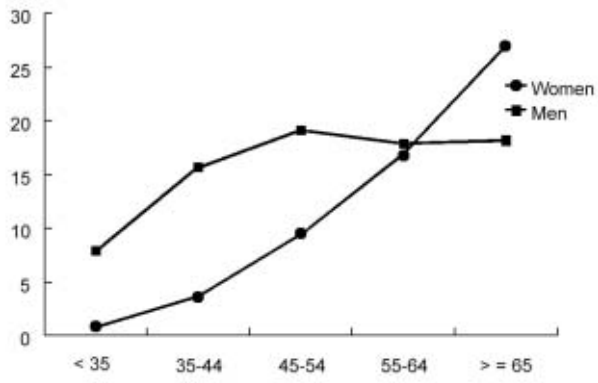

Figure 1. *Metabolic syndrome prevalence rates by gender and age groups in the study population.*

Table 1. Distribution of various atherosclerotic risk factors and C-reactive protein levels among health examination participants

	Women			Men			
	N	Mean	SD	N	Mean	SD	*p* value
Age	2650	51.3	12.8	3756	51.4	13.5	0.6766
Systolic blood pressure (mmHg)	2556	126.8	19.1	3734	129.8	16.8	< .0001
Diastolic blood pressure (mmHg)	2554	76.4	14.2	3726	80.0	13.5	< .0001
Body mass index (kg/m^2)	2648	23.5	3.7	3752	24.7	3.5	< .0001
Triglyceride (mg/dL)	2648	113.7	70.9	3755	142.1	110.4	< .0001
HDL cholesterol (mg/dl)	2492	56.5	14.4	3584	45.9	12.3	< .0001
LDL cholesterol (mg/dL)	2492	121.7	32.6	3579	126.6	32.2	< .0001
Fasting glucose (mg/dL)	2648	96.0	24.8	3748	98.5	26.0	< .0001
Total smoking amount in smokers (per day)	103	20.0	43.7	1416	24.3	30.3	0.0001
C-reactive protein (mg/dL)	2493	0.300	0.444	3582	0.3217	0.6971	0.1444
WBC count	2650	5995	1480	3755	6537	4280	< .0001

Table 2. Distribution of binary measures of risk factors among health examination participants

	Women, N = 2648 (%)	Men, N = 3756 (%)	*p* value
Hypercholesterolemia	12.31	10.20	0.0079
High LDL	12.60	14.47	0.0368
Low HDL	33.75	32.42	0.2794
Hypertriglyceridemia	9.71	17.31	< .0001
High BMI	28.17	43.66	< .0001
Smoking, ever	0.57	11.80	
Smoking, frequent	3.36	27.11	< .0001
Metabolic syndrome	14.94	22.60	< .0001

Table 3. Median and inter-quartile values of CRP levels (mg/L) among study participants according to the status of each component of the metabolic syndrome

CRP values (mg/L)	Risk Factor (-)			Risk Factor (+)			
Risk Factor	median	25^{th}	75^{th}	median	25^{th}	75^{th}	*p* value
Hyperglycemia	2.20	1.07	3.30	2.96	1.62	4.36	< .0001
Hypertension	2.11	0.50	3.17	2.46	1.30	3.77	< .0001
Obesity	2.16	0.50	3.25	2.90	1.71	4.33	< .0001
Hypertriglyceridemia	2.21	1.08	3.36	2.68	1.45	3.98	< .0001
Low HDL cholesterol	2.19	1.09	3.27	2.49	1.22	3.89	< .0001
Smoking	2.24	1.12	3.37	2.37	1.14	3.81	0.005

Table 4. Age, gender adjusted Spearman correlation coefficients and *p* values in atherosclerotic risk factors and CRP, WBC, and LDL-cholesterol levels among 5967 subjects

	Systolic blood pressure	Diastolic blood pressure	Body mass index	Total cholesterol	Triglyceride	HDL cholesterol	Fasting glucose	Numbers of metabolic syndrome
C-reactive protein	0.088	0.061	0.156	0.067	0.123	-0.081	0.110	0.161
	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001
LDL cholesterol	0.054	0.091	0.132	0.880	0.190	0.058	0.108	0.048
	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	0.000

0.464 mg/dL in elderly population ($p < 0.0001$). Table 3 shows the age- and gender-adjusted Spearman correlation coefficient(s) and respective *p* values for CRP and LDL cholesterol with metabolic syndrome risk factors. We found all CRP correlation coefficients were significantly different from zero, and the highest positive correlation was with BMI, and negative association with HDL cholesterol (Table 4). Furthermore, the age- and gender-adjusted Spearman correlation coefficients ranged between smoking amount and CRP varied in different ages, and they were 0.133 ($p = 0.051$) in elderly and 0.112 ($p < 0.0001$) in young group (data not shown). After adjusting for multiple variables such as gender and smoking status, high CRP levels were still strongly associated with metabolic syndrome status (Figure 2). The magnitude of odds ratio [OR] of CRP was higher in young than elderly generation (OR 1.39, 95% confidence interval [CI] 1.20-1.62 in young *vs*. OR 1.28, 95% CI 1.06-1.56 in elderly). The Hosmer-Lemeshow goodness of fit test was not significant, indicating the model fitting was acceptable.

DISCUSSION

Among Taiwanese population at risk of atherosclerosis, we clearly demonstrated that CRP was significantly associated with smoking and metabolic syndrome. There

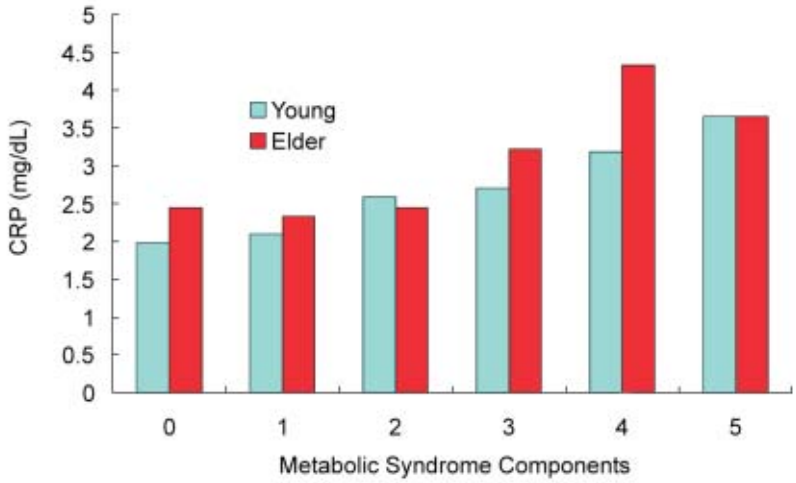

Figure 2. *Distribution of median CRP levels among study population according to presence of 0, 1, 2, 3, 4, or 5 components of metabolic syndrome, specified by age status. All p < 0.0001 by the Wilcox rank sum test.*

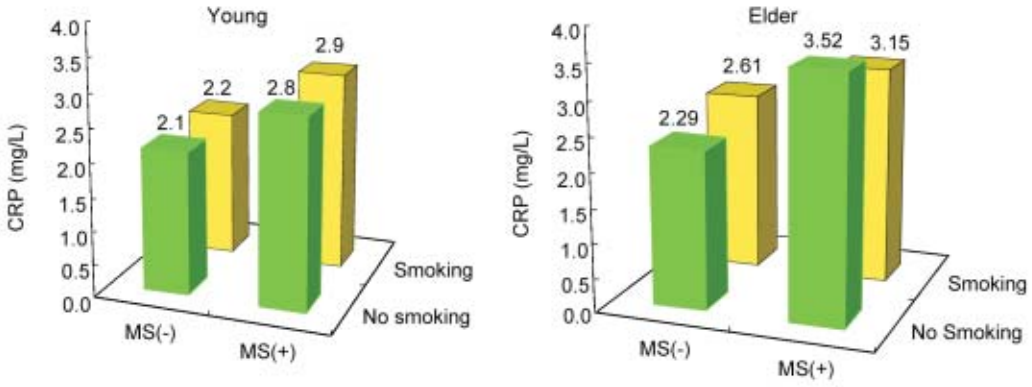

Figure 3. *Median C-reactive protein levels stratified by age, smoking, and metabolic syndrome status.*

existed differential correlation patterns between CRP and smoking, and it reached significant association only among young population. Also, we found in elderly population, the magnitude of CRP to predict metabolic syndrome was smaller than in young population. We concluded that in elderly population, factors other than smoking might change CRP levels and age-related process could weaken the influence of inflammation on atherosclerosis.

The relationship of smoking and CRP values was persistent across age, and more apparent among elder population (Figure 3). But the association of smoking vs. metabolic syndrome decreased progressively in elderly population. In elderly population, factors other than smoking might change metabolic syndrome status and age-related process could weaken the influence of inflammation on atherosclerosis.

There were several limitations in this study. First, this study was a prevalence study, and the associations identified cannot imply causation. Second, the definition of metabolic syndrome by body mass index, not by waist circumstance, can limit the applications in general population. Among the Asian population, body mass index was a poor indicator for body fat percentage,[18] although it was still a valuable indicator for a general obesity index.[19] Finally, we did not apply composite atherosclerotic risk scores for the population, and the relative importance of metabolic syndrome risk factors were unknown in the study subjects.[7]

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健康檢查族群之C反應蛋白，抽菸與代謝症候群之相關研究

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背景 C-反應蛋白被視為全身性發炎反應指標，但並不知道代謝症候群成份能預測 CRP 值的強度，同時抽菸及年齡的相互作用在 CRP 值的影響也並不清楚。

方法 我們收集在台灣某一三級教學醫院健康檢查中心自 2001 年 1 月到 12 月共 6406 成年人族群 (41.4%為女性)。高 CRP 值以族群 90th 百分 (5.31 mg/dL) 為切點，而代謝症候群則以修改的成人治療指引 III 內容決定。

結果 研究樣本中有 13.5%年齡大於 65 歲，而在抽菸行為方面，有 7.2%已戒菸，而 17.3% 仍有抽菸習慣。在調整性別及抽菸習慣後，平均 CRP 值在年輕人值為 3.43 mg/L，而老年人為 4.64 mg/L ($p < 0.0001$)。而代謝症候群的盛行率為 19.4%，在老年人盛行率比年輕人為高 (29.1% *vs.* 17.9%，$p < 0.0001$)。在調整性別，抽菸等多數之後，高的 CRP 值仍與代謝症候群有正向強度的相關性。

結論 CRP 與抽菸及代謝症候群有明顯的相關。在健康檢查族群中，發炎、抽菸及動脈硬化危險是互相牽連相關。

關鍵詞：C-反應蛋白、抽菸、代謝症候群、健康檢查。