Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 55 (2006) 415–421

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Association of C-reactive protein with the metabolic risk factors among young and middle-aged Koreans

Eun Young Choi[a], Eal Hwan Park[a], Yoo Seock Cheong[a], Insoo Rheem[b], Seouk Gun Park[c], Sunmi Yoo[d,*]

[a]*Department of Family Medicine, Dankook University College of Medicine, Cheonan 330-715, South Korea*
[b]*Department of Laboratory Medicine, Dankook University College of Medicine, Cheonan 330-715, South Korea*
[c]*Department of Nuclear Medicine, Dankook University College of Medicine, Cheonan 330-715, South Korea*
[d]*Department of Family Medicine, Inje University SanggyePaik Hospital, Seoul 139-707, South Korea*

Abstract

We investigated the relationship between the clustering of risk factors for metabolic syndrome and the plasma C-reactive protein (CRP) concentration as measured by high-sensitive CRP assay. Body mass index, waist circumference, triglycerides (TGs), high-density lipoprotein cholesterol, fasting glucose, systolic and diastolic blood pressures, insulin, and CRP were measured in 1046 Korean adults (560 males; age, 18-64 years) in 2003 to 2004. There were statistically significant positive correlations for log CRP with body mass index, waist circumference, log TG, log insulin, and log homeostasis model assessment in both sexes after adjusting for age and smoking status. High-density lipoprotein cholesterol showed a significant negative correlation with log CRP in both sexes. For both sexes, the mean level of log CRP increased with increasing number of risk factors of metabolic syndrome (P for trend $<.01$ for males and $<.001$ for females). Stepwise multivariate linear regression analysis showed that waist circumference contributed the largest portion of the variance in CRP levels in both sexes. Log homeostasis model assessment and log TG were independently associated with log CRP levels only in females. These results indicate that CRP, a marker of inflammation that underlies atherosclerosis, is associated with the clustering of each metabolic syndrome risk factor and, furthermore, that abdominal obesity is the strongest predictor of CRP level in the Korean adult population.

1. Introduction

Inflammation has been suggested as a risk factor for the development of atherosclerosis [1,2]. C-reactive protein (CRP), an acute-phase reactant and sensitive marker of subclinical inflammation, has proven to be a strong and independent predictor of both diabetes [3-7] and cardiovascular disease [8-12].

Metabolic syndrome, which is characterized by the clustering of abdominal obesity, hypertension, impaired glucose tolerance, and atherogenic dyslipidemia, is associated with increased risk of cardiovascular disease [13]. The more risk factors cluster, the greater risk of cardiovascular disease [14-16]. Recent studies have shown that elevated CRP is strongly associated with various characteristics of the metabolic syndrome [17-22]. Previous studies on the relationship of CRP and the metabolic syndrome, however, focused on the individual risk factors of metabolic syndrome, not the clustering of various risk factors [23-27]. In addition, little is known about this relationship in Asian people who exhibit more metabolic complications associated with obesity even at lower body mass index (BMI) than whites do [28-32]. Therefore, we investigated the association between plasma CRP concentration and the risk factors of metabolic syndrome in the Korean adult population.

2. Subjects and methods

The study population consisted of 1224 Korean men and women who visited Dankook University Hospital for health examination from December 2003 to January 2004. They responded to a self-reported questionnaire and underwent a physical examination, including height and weight, and blood pressure measured sitting after 5 minutes of rest, and

* Corresponding author. Tel.: +82 2 950 1150; fax: +82 2 950 1955.
E-mail address: sunmiyoo@hanafos.com (S. Yoo).

0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.11.002

provided a collection of fasting blood samples. We excluded 25 subjects with CRP level of 10 mg/L or higher, indicating clinically relevant inflammatory conditions; 52 subjects with diagnosed diabetes, fasting glucose of 126 mg/dL or higher, and diabetes medication; 44 subjects who were older than 65 years; and a further 57 subjects with a missing value for smoking status, which is an important confounding factor for CRP concentration. Consequently, the current analysis was confined to 560 men and 486 women with complete data on all components of the metabolic syndrome and serum CRP concentration.

2.1. Definition

Characteristics of the metabolic syndrome were based on the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) using the following cutoff limits: (1) blood pressure of 135/85 mm Hg or higher; (2) triglyceride (TG) of 1.7 mmol/L or higher (150 mg/dL); (3) low high-density lipoprotein cholesterol (HDL-C) of less than 1.0 mmol/L (40 mg/dL) for men and less than 1.3 mmol/L (50 mg/dL) for women; and (4) fasting glucose of 6.1 mmol/L or higher (110 mg/dL) [13]. Abdominal obesity was defined by Asia-Pacific cutoff limits: waist circumference of 90 cm or more for men and 80 cm or more for women because the importance of ethnic-specific cutoff points for waist circumference as a measure of central adiposity was recognized. Subjects with 3 or more risk factors of the above criteria were diagnosed as having the metabolic syndrome.

If the participants were using antihypertensive medication, they were considered as participants with high blood pressure. Obesity was defined as BMI of 25 kg/m^2 or higher according to the Asia-Pacific criteria [33]. Smoking was classified into "nonsmoker," "former smoker," and "current smoker." Insulin resistance was assessed from fasting glucose and insulin values using the following homeostasis model assessment (HOMA) calculation: insulin resistance = [fasting insulin (μIU/mL) × fasting glucose (mmol/L)]/22.5. This formula moderately agreed with the hyperinsulinemic euglycemic clamp [34] in Korean population [35].

Table 1
Clinical and biochemical characteristics of subjects

Variable	Male (n = 560)	Female (n = 486)	*P*
Age, mean ± SD (y)	42.7 ± 9.0	42.1 ± 10.2	NS
BMI, mean ± SD (kg/m^2)[a]	24.0 ± 2.9	22.9 ± 2.8	<.001
Waist circumference, mean ± SD (cm)[a]	84.8 ± 8.0	78.1 ± 8.0	<.001
HDL-C, mean ± SD (mg/dL)[a]	47.1 ± 10.7	53.5 ± 12.1	<.001
Fasting glucose, mean ± SD (mg/dL)[a]	90.7 ± 10.0	88.0 ± 8.3	<.001
TG, median (IQR) (mg/dL)[b]	130 (93-185)	96 (69-140)	<.001
Systolic blood pressure, mean ± SD (mm Hg)[a]	121.8 ± 12.8	118.0 ± 13.5	<.001
Diastolic blood pressure, mean ± SD (mm Hg)[a]	83.3 ± 8.8	79.2 ± 8.9	<.001
HOMA, median (IQR)[b]	0.5 (0.2-1.2)	0.2 (0.2-1.0)	<.01
Insulin, median (IQR) (μIU/mL)[b]	2.4 (0.9-5.3)	0.9 (0.9-4.8)	<.01
CRP, median (IQR) (mg/L)[b]	0.6 (0.3-1.3)	0.4 (0.2-0.9)	<.001
Smoking status (%)[c]			<.001
Never	23.8	49.8	
Former	25.4	43.2	
Current	50.8	7.0	
Medication (%)[b]			NS
Hypertension	4.9	6.2	

[a] *t* Test.
[b] Mann-Whitney *U* test.
[c] χ^2 Test.

Table 2
Partial Spearman correlation coefficients between log CRP and variables of metabolic syndrome adjusted for age and smoking status

Variable	Men	Women
BMI	0.20**	0.34**
Waist circumference	0.22**	0.28**
HDL-C	−0.15**	−0.16**
Log TG	0.12*	0.21**
Fasting glucose	0.03	0.16**
Systolic blood pressure	0.05	0.09
Diastolic blood pressure	0.01	0.09
Log HOMA	0.13*	0.21**
Log insulin	0.13*	0.20**

* $P < .01$.
** $P < .001$.

2.2. Laboratory measurements

Venous blood samples were collected from each subject after a 12-hour fast and used for assay of glucose, total cholesterol and HDL-C, and TG. Total cholesterol and TG were determined enzymatically. High-density lipoprotein cholesterol was measured with phosphotungstate method. Glucose was enzymatically determined with hexokinase method. Insulin was measured with immunoradiometric assay. C-reactive protein was measured with latex-enhanced immunonephelometry, on a Behring BNII Nephelometer (Dade Behring, Newark, DE). This assay used a calibrator traceable to World Health Organization Reference Material (Certified Reference Material 470). The lower detection limit of the assay was 0.16 mg/L. Undetectable CRP values were recorded as 0.16 mg/L. The intra- and interassay coefficients of variation for CRP were 4.0% and 2.6%, respectively.

2.3. Data analysis

The clinical and biochemical features of the population were presented as mean ± SD, median (interquartile range [IQR]), or percentages. Because the distributions of CRP, insulin, TG, and HOMA were highly skewed, these variables were natural log-transformed for all other analyses. All analyses were done separately by sex because mean CRP levels differed by sex in the present population. Age and smoking status were the determinants of CRP levels in

Table 3
Geometric means of CRP (mg/L) adjusted for age and smoking status and 95% confidence interval (CI) for the variables of metabolic syndrome in men

Variable	n	Geometric means of CRP (95% CI)	P
Obesity (BMI ≥ 25 kg/m²)			
Yes	200	0.9 (0.7-1.0)	<.001
No	360	0.6 (0.5-0.7)	
Abdominal obesity (waist circumference >90 cm)			
Yes	407	0.7 (0.7-0.8)	<.001
No	153	0.6 (0.5-0.6)	
High blood pressure (≥ 130/85 mm Hg or antihypertensive medication)			
Yes	281	0.7 (0.7-0.8)	.086
No	279	0.6 (0.6-0.7)	
Low HDL-C (<40 mg/dL)			
Yes	137	0.8 (0.7-1.0)	<.05
No	423	0.6 (0.6-0.7)	
Hyperglycemia (fasting glucose ≥ 110 mg/dL)			
Yes	29	1.0 (0.7-1.4)	<.05
No	531	0.7 (0.6-0.7)	
High TG (≥ 150 mg/dL)			
Yes	225	0.8 (0.7-0.9)	<.05
No	335	0.6 (0.6-0.7)	

Data were calculated using analysis of covariance.

previous reports [25,26,36], and CRP levels also differed by age and smoking status in the present population; therefore, multivariate models were tailored to account for these possible confounders. Partial Spearman correlation coefficients adjusted for age and smoking status were calculated for CRP with variables of metabolic syndrome components, log insulin, and log HOMA. The adjusted mean values of log CRP according to the number of metabolic disorders were calculated by analysis of covariance. Using a general linear model, we tested the linear trends for increasing log CRP levels across the number of metabolic risk factors.

Next, stepwise multivariate linear regression analysis was fit for log CRP as a dependent variable to demonstrate the relative contribution of each of the metabolic syndrome risk factors to CRP. After age and smoking status were forced into the model as confounders, the following variables were included into the model: components of metabolic syndrome from ATP III (waist circumference, systolic blood pressure, HDL-C, log TG, and fasting glucose) and log HOMA. All statistical analyses were performed using the SPSS statistical software (version 11.5, SPSS, Chicago, IL).

3. Results

Table 1 presents the demographic and clinical characteristics of the 1046 subjects. Mean age of male and female subjects was 42.7 years (SD, 9.0 years) and 42.1 years (SD, 10.2 years), respectively (range, 18-64 years). The plasma concentration of CRP in males was significantly higher than in females (median, 0.6 mg/L [IQR, 0.3-1.3 mg/L] vs median, 0.4 mg/L [IQR, 0.2-0.9 mg/L]; $P < .001$). The geometric mean plasma concentrations of CRP according to the smoking status were highest among current smokers and lowest among nonsmokers in both male and female subjects (data not shown).

Partial Spearman rank correlation coefficients of log CRP with variables of the metabolic syndrome adjusted for age and smoking status are shown in Table 2. There were statistically significant positive correlations in both sexes for CRP with BMI, waist circumference, log TG, log insulin, and log HOMA. However, there was a significant negative correlation of log CRP with HDL-C in both sexes ($P < .001$). The strongest correlation was observed between log CRP and BMI in females ($r = 0.34$, $P < .001$) and between log CRP and waist circumference in males ($r = 0.22$, $P < .001$).

The geometric mean CRP levels in subjects with each risk factor of metabolic syndrome were significantly higher in both sexes than in subjects without risk factors after adjusting for age and smoking status (Tables 3 and 4). Nevertheless, the geometric mean CRP levels of male subjects with high blood pressure defined by ATP III criteria were not significantly different from those of males with normal blood pressure (Table 3). The geometric mean CRP levels of female subjects with high fasting glucose were not significantly different from those of females with normal blood glucose (Table 4).

The mean levels of log CRP (SD) for those with 0, 1, 2, 3, and more than 4 components of the metabolic syndrome

Table 4
Geometric means of CRP (mg/L) adjusted for age and smoking status and 95% CI for the variables of metabolic syndrome in women

Variable	n	Geometric means of CRP (95% CI)	P
Obesity (BMI ≥ 25 kg/ m²)			
Yes	107	0.9 (0.7-1.1)	<.001
No	379	0.4 (0.4-0.4)	
Abdominal obesity (waist circumference > 80 cm)			
Yes	185	0.7 (0.6-0.8)	<.001
No	301	0.4 (0.4-0.5)	
High blood pressure (≥ 130/85 mm Hg or antihypertensive medication)			
Yes	163	0.6 (0.5-0.7)	.001
No	323	0.4 (0.4-0.5)	
Low HDL-C (<50 mg/dL)			
Yes	198	0.6 (0.6-0.7)	<.001
No	288	0.4 (0.4-0.4)	
Hyperglycemia (fasting glucose ≥ 110 mg/dL)			
Yes	7	0.8 (0.4-1.6)	.206
No	479	0.5 (0.4-0.5)	
High TG (≥ 150 mg/dL)			
Yes	104	0.7 (0.6-0.8)	<.001
No	382	0.4 (0.4-0.5)	

Data were calculated using analysis of covariance.

were −0.66 (1.01), −0.59 (1.00), −0.30 (0.96), 0.27 (0.94), and 0.02 (0.84) mg/L in males, and −1.18 (0.76), −0.92 (0.93), −0.46 (1.01), −0.07 (1.02), and −0.04 (0.98) mg/L in females, respectively. There was a linear increase in log CRP with the increasing number of metabolic syndrome risk factors in both sexes (P for trend <.001 for males and <.001 for females) (Fig. 1A and B).

The relative contribution of each component of metabolic syndrome to CRP level was examined by stepwise linear regression analysis. After age and smoking status were forced into the model, the following variables were assessed: waist circumference, log TG, fasting blood glucose, systolic blood pressure, HDL-C, and log HOMA. Only those variables with a P value of less than .05 were included in the final fitted model. Stepwise multivariate linear regression analysis showed that waist circumference was independently associated with log CRP levels in males, whereas waist circumference, log HOMA, and log TG were associated in females. The model R^2 was 8.2% for male subjects and 19.5% for female subjects. Waist circumference had the largest partial R^2 in both men and women (Table 5).

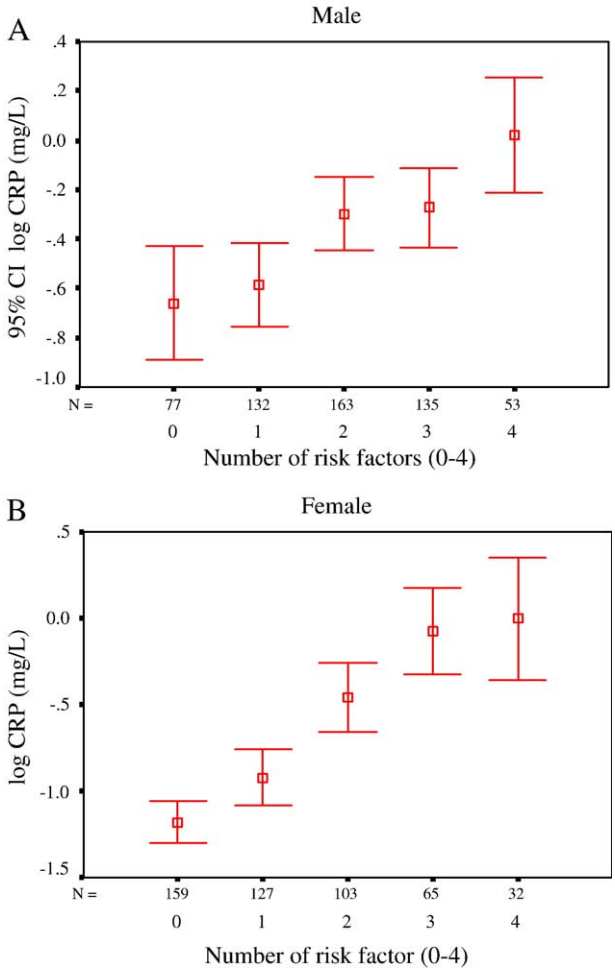

Fig. 1. Mean levels of log CRP and 95% CI adjusted for age and smoking status according to the number of components of the metabolic syndrome. A, Mean log CRP levels adjusted for age and smoking status in males (P_{trend} < .001 by GLM). B, Mean log CRP levels adjusted for age and smoking status in females (P_{trend} < .001 by General Linear Model).

Table 5
Stepwise multiple linear regression analysis with log CRP as dependent variable

Variable	β	SE (β)	P	Partial R^2 (%)
Male				
Waist circumference	.027	.005	.000	5.0
Female				
Waist circumference	.028	.006	.000	9.5
Log HOMA	.167	.042	.000	3.3
Log TG	.217	.097	.026	1.4

A final predictive model was derived by stepwise linear regression analysis. After age and smoking status were forced into the model, the following candidate independent variables were assessed: waist circumference, log TG, fasting blood glucose, systolic blood pressure, HDL-C, and log HOMA. Only those variables with a P value of less than .05 were included in the final fitted model. The model R^2 for male subjects was 8.2% and for female subjects was 19.5%. β indicates linear regression coefficient.

4. Discussion

The present study has demonstrated that CRP, a sensitive marker of inflammation, was associated with metabolic syndrome in the Korean adult population. After adjustment for age and smoking status, the geometric mean CRP levels in both sexes were significantly higher in those subjects who had each characteristic of the metabolic syndrome than in those who did not, except for males with high blood pressure and except for females with high fasting glucose. Previous studies [17-22] have shown that CRP levels are strongly associated with various characteristics of the metabolic syndrome, as has our present study. Only in male subjects with high blood pressure and in female subjects with high fasting glucose were the geometric mean CRP levels not significantly higher than in those with normal blood pressure and normal fasting glucose. These differences may have been caused by the single blood pressure measurement and small number of female subjects with high fasting glucose.

There was a strong linear increase in log CRP in both sexes as the number of components of metabolic disorders increased. Previous studies have shown a positive association between CRP and components of the metabolic syndrome cluster. Tamakoshi et al [21] reported that the odds ratio for elevated CRP is increased with an increasing number of metabolic syndrome factors. Aronson et al [20], Festa et al [17], and Frohlich et al [18] also showed that there is a strong linear increase in log CRP with an increasing number of metabolic syndrome factors among various populations, as we found with young and middle-aged Koreans. The mechanism through which each component of metabolic syndrome increases CRP levels directly has not yet been established. Each component of metabolic syndrome is a well-known risk factor in the atherosclerotic

process. Our results suggest that metabolic syndrome, especially the clustering of its components, is associated with a systemic low-grade inflammation, which causes the progression of atherosclerosis.

Multiple linear regression analysis, which uses log CRP levels as the dependent variable and all components of metabolic syndrome and log HOMA as the independent variable, showed that waist circumference contributes most of the variance in CRP levels in both males and females. Because many other factors than metabolic risk variables such as sex, smoking, age, ethnicity, insulin resistance, and nonspecific inflammation may affect the level of CRP, the total variance of CRP explained by them was small. Our finding suggests that the centrally distributed body fat, as evaluated by waist circumference, is a stronger predictor of CRP level than other components of the metabolic syndrome and insulin resistance, as measured by HOMA. The association between central adiposity and increased CRP has been noted in previous studies [17-19]. Experimental studies suggest that abdominal adipose tissue is a major source of cytokines, including interleukin 6, which is an important determinant of hepatic CRP synthesis [22,37]. Because waist circumference is the best surrogate of visceral adiposity across a wide age range [38], it is possible to say that CRP level is significantly associated with visceral adipose tissue, as evaluated by waist circumference, in Korean subjects. In other words, accumulation of visceral adipose tissue is a key factor of both features of the metabolic syndrome and low-grade chronic inflammation. Findings from other studies that CRP levels decreased in response to weight loss [39-44] also support our results.

Some studies have described an independent inverse association between measures of insulin resistance and CRP [4,45]. By contrast, other studies failed to identify a relationship between serum markers of inflammation and measures of insulin resistance after controlling for the effect of obesity [20,46-48]. In our study, log HOMA was independently associated with CRP only in females. Nevertheless, its contribution was also small compared with waist circumference. Future research is needed to identify the relationship between insulin resistance and CRP independent of body mass.

Our study had a few limitations. First, as the study subjects comprised only those who visited the hospital for a routine health check, the findings might not be generalized to the general Korean population. Second, CRP levels in women were low compared with other studies in western countries [49-51]. Our study population of women were relatively healthy and young, and had smaller BMI (only 23.5% of women had BMI >25) compared with those in studies from western countries [49], and ethnic differences between whites and Asians [12] including Koreans might have contributed this difference. Third, the levels of fasting insulin were extremely low compared with other studies. It may be related with the variability of insulin measurements from different laboratories [52]. Relatively lean and young subjects in our studies than in other studies from western countries may contribute to these low insulin levels. Lastly, the HOMA, as a marker of insulin resistance, only showed moderate association in Korean population including diabetic subjects. Further studies are needed to examine the association of the HOMA and the hyperinsulinemic euglycemic clamp in nondiabetic Korean population.

In conclusion, we found that CRP level was associated with the clustering of each metabolic syndrome risk factor and that waist circumference was the strongest predictor of CRP levels in Korean adults. This finding suggests that metabolic syndrome is associated with a systemic inflammatory response, which plays an important pathogenetic role in atherothrombotic disease. We can confidently conclude that reducing waist circumference is probably the most important intervention to ameliorate the proinflammatory state associated with the metabolic syndrome.

Acknowledgment

This study was supported by a grant from the Korean Obesity Society of Family Medicine (2003-1).

The authors thank Dr Jong Sung Kim and Professor Yong Gyu Park for their statistical advice.

References

[1] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-26.

[2] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.

[3] Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, et al. The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. Diabetes 2001;50:2384-9.

[4] Festa A, D'Agostino R Jr, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor–1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes 2002;51:1131-7.

[5] Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes 2002;51:1596-600.

[6] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.

[7] Thorand B, Lowel H, Schneider A, Kolb H, Meisinger C, Frohlich M, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Arch Intern Med 2003;163:93-9.

[8] Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;144:537-47.

[9] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.

[10] Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the cardiovascular health study and

the rural health promotion project. Arterioscler Thromb Vasc Biol 1997;17:1121-7.
[11] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
[12] Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199-204.
[13] Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[14] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
[15] Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414-9.
[16] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
[17] Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42-7.
[18] Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 2000;23:1835-9.
[19] Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC, et al. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol 1999;19:1986-91.
[20] Aronson D, Bartha P, Zinder O, Kerner A, Markiewicz W, Avizohar O, et al. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. Int J Obes Relat Metab Disord 2004;28:674-9.
[21] Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, et al. The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 2003;27:443-9.
[22] Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972-8.
[23] Mendall MA, Patel P, Ballam L, Strachan D, Northfield MA. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ 1996;312:1061-5.
[24] Mendall MA, Strachan DP, Butland BK, Ballam L, Morris J, Sweetnam PM, et al. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur Heart J 2000;21:1584-90.
[25] Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol 1999;84:1018-22.
[26] Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis 2003;167:73-9.
[27] Williams MJ, Williams SM, Milne BJ, Hancox RJ, Poulton R. Association between C-reactive protein, metabolic cardiovascular risk factors, obesity and oral contraceptive use in young adults. Int J Obes Relat Metab Disord 2004;28:998-1003.
[28] Kim Y, Suh YK, Choi H. BMI and metabolic disorders in South Korean adults: 1998 Korea National Health and Nutrition Survey. Obes Res 2004;12:445-53.
[29] Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. Int J Obes Relat Metab Disord 1999;23:1136-42.
[30] Thomas GN, Ho SY, Lam KS, Janus ED, Hedley AJ, Lam TH. Impact of obesity and body fat distribution on cardiovascular risk factors in Hong Kong Chinese. Obes Res 2004;12:1805-13.
[31] Lee ZS, Critchley JA, Ko GT, Anderson PJ, Thomas GN, Young RP, et al. Obesity and cardiovascular risk factors in Hong Kong Chinese. Obes Rev 2002;3:173-82.
[32] Lee SH, Kim YS, Sunwoo S, Huh BY. A retrospective cohort study on obesity and hypertension risk among Korean adults. J Korean Med Sci 2005;20:188-95.
[33] WHO West Pacific Region. The Asia-Pacific perspective: refining obesity and its treatment. IOTF Feb. 2000.
[34] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
[35] Kang ES, Yun YS, Park SW, Kim HJ, Ahn CW, Song YD, et al. Limitation of the validity of the homeostasis model assessment as an index of insulin resistance in Korea. Metabolism 2005;54:206-11.
[36] Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, et al. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. Arterioscler Thromb Vasc Biol 1997;17:2167-76.
[37] Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor–alpha, in vivo. J Clin Endocrinol Metab 1997;82:4196-200.
[38] Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. Int J Obes Relat Metab Disord 2004;28:1018-25.
[39] O'brien KD, Brehm BJ, Seeley RJ, Bean J, Wener MH, Daniels S, et al. Diet-induced weight loss is associated with decreases in plasma serum amyloid a and C-reactive protein independent of dietary macronutrient composition in obese subjects. J Clin Endocrinol Metab 2005;90:2244-9.
[40] Ryan AS, Nicklas BJ. Reductions in plasma cytokine levels with weight loss improve insulin sensitivity in overweight and obese postmenopausal women. Diabetes Care 2004;27:1699-705.
[41] Valsamakis G, McTernan PG, Chetty R, Al Daghri N, Field A, Hanif W, et al. Modest weight loss and reduction in waist circumference after medical treatment are associated with favorable changes in serum adipocytokines. Metabolism 2004;53:430-4.
[42] Marfella R, Esposito K, Siniscalchi M, Cacciapuoti F, Giugliano F, Labriola D, et al. Effect of weight loss on cardiac synchronization and proinflammatory cytokines in premenopausal obese women. Diabetes Care 2004;27:47-52.
[43] Kopp HP, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, et al. Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. Arterioscler Thromb Vasc Biol 2003;23:1042-7.
[44] Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 2003;289:1799-804.
[45] McLaughlin T, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P, et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908-12.
[46] Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in

Europeans and South Asians. Int J Obes Relat Metab Disord 2001;25:1327-31.

[47] Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res 2001;9:414-7.

[48] Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Sancho J, San Millan JL. Obesity, and not insulin resistance, is the major determinant of serum inflammatory cardiovascular risk markers in pre-menopausal women. Diabetologia 2003;46:625-33.

[49] Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282:2131-5.

[50] Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Circulation 2004;109:706-13.

[51] Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol 2002;22:1668-73.

[52] Robbins DC, Andersen L, Bowsher R, Chance R, Dinesen B, Frank B, et al. Report of the American Diabetes Association's Task Force on standardization of the insulin assay. Diabetes 1996;45:242-56.