Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 983–988
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Association of soluble intercellular adhesion molecule–1 with insulin resistance and metabolic syndrome in Taiwanese

Lung-An Hsu[a], Yu-Lin Ko[b,*], Semon Wu[c], Ming-Sheng Teng[c], Hsin-Hua Chou[b], Chi-Jen Chang[a], Pi-Yueh Chang[d]

[a]*The First Cardiovascular Division, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei 105, Taiwan*
[b]*The Division of Cardiology, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Taipei branch, Xindian City, Taipei 231, Taiwan*
[c]*Department of Medical Education and Research, Buddhist Tzu Chi General Hospital, Taipei branch, Taipei 231, Taiwan*
[d]*Department of Pathology, Chang Gung Memorial Hospital, Taipei, Taiwan*

Received 8 October 2008; accepted 17 February 2009

Abstract

Circulating concentrations of soluble cell adhesive molecules are useful predictors for the risk of development and progression of atherosclerosis. This study was initiated to investigate the association between soluble intercellular adhesive molecule–1 (sICAM-1) levels and traditional and emerging cardiovascular risk factors, as well as insulin resistance and metabolic syndrome, in a Taiwanese population. Six hundred nine unrelated individuals recruited during routine health examinations were enrolled for the analysis. In age- and sex-adjusted regression models, sICAM-1 levels were negatively associated with high-density lipoprotein cholesterol levels and positively associated with systolic, mean, and diastolic blood pressure; body mass index; waist circumference; waist-hip ratio; the homeostasis model assessment index; fasting serum insulin; triglyceride; and C-reactive protein levels. The sICAM-1 levels were also higher in subjects with current smoking ($P = .001$), diabetes mellitus ($P = .004$), insulin resistance ($P < .001$), and metabolic syndrome ($P < .001$). The sICAM-1 levels increased in a stepwise fashion with increasing Framingham risk score quartiles ($P = .001$) and with increasing number of metabolic syndrome components ($P < .001$). In subjects with metabolic syndrome, increased C-reactive protein levels were associated with increased sICAM-1 levels ($P = .003$). In stepwise linear regression models, sICAM-1 levels remained associated with current smoking, insulin resistance, and metabolic syndrome. In conclusion, our data revealed that insulin resistance and metabolic syndrome were associated with sICAM-1 levels in Taiwanese. These data provide further evidence of the mechanisms of sICAM-1 as a molecular marker for atherosclerosis.

1. Introduction

Atherosclerosis and its sequelae remain the leading cause of morbidity and mortality in Western countries and in Taiwan [1,2]. The risk of atherosclerotic cardiovascular diseases is higher in subjects with conventional and emerging risk factors as well as in subjects with insulin resistance and metabolic syndrome. Low-grade inflammation is one of the emerging risk factors implicated in the development of atherosclerosis [3]. One early phase of atherosclerosis involves the recruitment and transendothelial migration of inflammatory cells from the circulation. Several lines of evidence support a crucial role of adhesive molecules in the development of atherosclerosis and plaque instability [4-6].

Intercellular adhesion molecule–1 (ICAM-1) is an adhesive molecule of the immunoglobulin superfamily that is regulated by proinflammatory cytokines and has been observed in atherosclerotic plaques. Soluble intercellular adhesion molecule–1 (sICAM-1) represents a circulating form of ICAM-1 that is constitutively expressed or is inducible on the cell surface of different cell lines. Epidemiologic studies have shown that plasma concentrations of sICAM-1 are elevated in patients with unstable angina and myocardial infarction [7,8]. Recent prospective studies also indicate that elevated baseline levels of sICAM-1 are associated with increased risk for future coronary events in healthy individuals and in patients at

* Corresponding author. Tel.: +886 2 6628 9779x5709; fax: +886 2 6628 9009.
E-mail address: yulinkotw@yahoo.com.tw (Y.-L. Ko).

0026-0495/$ – see front matter © 2009 Published by Elsevier Inc.
doi:10.1016/j.metabol.2009.02.021

risk of or with established coronary artery disease [9-13]. Many recent studies have investigated the relations between soluble adhesion molecule levels and potential variation of risk factors in healthy populations; however, the results have been controversial [13-18]. Previous studies have shown a cumulative impact of multiple risk factors on sICAM-1 plasma concentration by using established or major risk factors and Framingham risk scores [14,16,18]. Therefore, the aim of the present study is to identify the major factors associated with high sICAM-1 levels, including insulin resistance and metabolic syndrome, in a Taiwanese population.

2. Subjects and methods

2.1. Study population

The study subjects who had no known history of major systemic and cardiovascular diseases were recruited during routine health examinations. Exclusion criteria included a history of myocardial infarction, stroke, or transient ischemic attack; cancer; and current renal or liver disease. Two subjects with very high sICAM-1 levels of more than 1000 ng/mL were excluded from the analysis. Overall, 609 study subjects (323 men with a mean age of 45.1 ± 10.4 years; 286 women with a mean age of 46.9 ± 10.1 years) were enrolled in the analysis. The clinical and biometric features of the study population are summarized in Table 1. *Hypertension* was defined according to the following criteria: (1) systolic blood pressure (BP) of at least 140 mm Hg, diastolic BP of at least 90 mm Hg, or both or (2) receiving long-term antihypertensive treatments. *Diabetes mellitus* was defined as blood glucose levels before a meal of at least 126 mg/dL or receiving regular antidiabetic medications. *Obesity* was defined as a body mass index (BMI) of 25 kg/m^2 or more according to the Asian criteria [19]. A *current smoker* was defined as a subject who continued smoking cigarette regularly. A *past smoker* was defined as a subject who had discontinued smoking for more than 1 year. The homeostasis model assessment (HOMA) index was calculated with the following formula: fasting serum insulin (microunits per milliliter) × fasting plasma glucose (millimoles per liter)/22.5. Insulin resistance was recognized when the HOMA index reached the upper quartile. Subjects with 3 or more of the following attributes are typically defined as having the *metabolic syndrome*: (1) BP of at least 130/85 mm Hg and/or taking medication for hypertension, (2) triglycerides of at least 150 mg/dL, (3) high-density lipoprotein (HDL) cholesterol less than 40 mg/dL for men and less than 50 mg/dL for women, (4) fasting plasma glucose of at least 110 mg/dL and/or taking medication for diabetes mellitus, and (5) waist circumference greater than 90 cm for men and greater than 80 cm for women (modified criteria for Asians [19]). The Framingham risk score was calculated as

Table 1
Baseline characteristics of study subjects

	Total	Male	Female	*P* value
n	609	323	286	<.001
Age	45.9 ± 10.3	45.1 ± 10.4	46.9 ± 10.1	.031
Cholesterol, mg/dL	198.3 ± 36.8	199.7 ± 37.4	196.7 ± 36.1	.316
Triglycerides, mg/dL	142.0 ± 117.8	169.8 ± 145.5	110.6 ± 61.6	<0001
LDL cholesterol, mg/dL	115.8 ± 33.0	117.8 ± 34.0	113.5 ± 31.7	.109
HDL cholesterol, mg/dL	55.1 ± 14.1	49.8 ± 11.7	61.1 ± 14.2	<0001
Systolic BP, mm Hg	115.3 ± 17.6	116.3 ± 16.4	114.1 ± 18.8	.142
Diastolic BP, mm Hg	76.0 ± 10.6	78.0 ± 10.4	73.9 ± 10.3	<0001
Mean BP, mm Hg	89.1 ± 12.0	90.7 ± 11.5	87.3 ± 12.4	<0001
Fasting plasma glucose, mg/dL	97.2 ± 23.9	99.7 ± 26.3	94.4 ± 20.4	.006
Fasting serum insulin, μU/mL	9.37 ± 5.25	10.03 ± 6.14	8.61 ± 3.90	.001
HOMA index	2.29 ± 1.59	2.51 ± 1.84	2.04 ± 1.19	<0001
Diabetes mellitus, %	2.6%	2.8%	2.4%	.499
Hypertension, %	19.5%	20.4%	18.5%	.313
Obesity, %	39.7%	47.7%	30.8%	<0001
Smokers, %	19.0%	32.8%	3.5%	<0001
BMI, kg/m^2	24.3 ± 3.5	25.0 ± 3.1	23.6 ± 3.7	<0001
Waist-hip ratio	0.87 ± 0.06	0.89 ± 0.05	0.85 ± 0.07	<0001
Waist circumference, cm	85.3 ± 9.6	88.1 ± 7.7	82.1 ± 10.4	<0001
CRP, mg/L	1.68 ± 6.20	1.92 ± 8.00	1.41 ± 3.11	.162
Fibrinogen, mg/dL	265.5 ± 70.0	263.4 ± 71.9	267.9 ± 67.7	.431
Homocysteine, μmol/L	10.3 ± 5.3	11.6 ± 5.0	8.9 ± 5.4	<0001
Lp(a), mg/dL	20.4 ± 20.5	20.3 ± 21.0	20.6 ± 19.8	.664
SAA,[a] μg/mL	6.12 ± 15.42	7.03 ± 19.47	5.11 ± 8.90	.114
sICAM-1, ng/mL	238.9 ± 100.4	242.2 ± 98.9	235.3 ± 102.1	.399

Triglyceride, CRP, and Lp(a) were logarithmically transformed before statistical analysis to adhere to a normality assumption; untransformed data are however shown.

[a] Only 601 individuals.

described previously [16]. The study protocol was approved by the ethics committee of Chang Gung Memorial Hospital, and informed consent was obtained from all subjects.

2.2. Assays

Most markers were measured with sandwich enzyme-linked immunosorbent assay methods developed in-house; this included C-reactive protein (CRP), serum amyloid A (SAA), homocysteine, and sICAM-1. All in-house kits were compared with commercial enzyme-linked immunosorbent assay kits and showed good to excellent correlation [20,21]. Serum insulin levels were measured using an immunoradiometric assay (Bio-source, Nivelles, Belgium). Glucose was enzymatically determined by using the hexokinase method. Lipoprotein (a) (Lp[a]) was measured using a turbidimetric assay on the Hitachi-7600 analyzer (Tokyo, Japan). Total cholesterol and triglyceride concentrations were measured by automatic enzymatic colorimetry. High-density lipoprotein cholesterol levels were measured enzymatically after phosphotungsten/magnesium precipitation. Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald formula. Plasma fibrinogen level was determined using the Clauss method adapted for a Sysmex CA1-1500 instrument (Kobe, Japan) in the Clinical Hematology Laboratory.

2.3. Laboratory examination

Before starting the study, all subjects underwent an initial screening assessment that included a medical history, vital signs, a 12-lead electrocardiogram, measurement of lipid variables, and emerging risk factors. For analysis, 10 mL of venous blood was taken by venipuncture in the morning before breakfast after an overnight (8-12 hours) fast. Venous blood samples were drawn from an antecubital vein with a 21-gauge needle without venous stasis. Serum and plasma samples were centrifuged at 3000*g* for 15 minutes at 4°C. Immediately after centrifugation, the serum/plasma samples were frozen and stored at −80°C before analysis. All measurements were performed in a central laboratory.

Table 2
Unadjusted and age- and sex-adjusted correlation coefficients between sICAM-1 levels and measured cardiovascular risk factors

Risk factor	Unadjusted		Adjusted for age and sex	
	r	*P* value	*r*	*P* value
Age	0.06	.134		
Cholesterol, mg/dL	0.047	.249	0.035	.384
Triglycerides, mg/dL	0.158	<.001	0.148	<.001
LDL cholesterol, mg/dL	0.031	.439	0.019	.639
HDL cholesterol, mg/dL	−0.125	.002	−0.132	.001
Systolic BP, mm Hg	0.134	.001	0.115	.004
Diastolic BP, mm Hg	0.133	.001	0.115	.005
Mean BP, mm Hg	0.140	.001	0.121	.003
Fasting plasma glucose, mg/dL	0.059	.147	0.040	.328
Fasting serum insulin, μU/mL	0.169	<.001	0.169	<.001
HOMA index	0.176	<.001	0.171	<.001
BMI, kg/m^2	0.109	.007	0.097	.017
Waist circumference, cm	0.114	.005	0.097	.017
Waist-hip ratio	0.098	.016	0.077	.057
CRP, mg/L	0.181	<.001	0.173	<.001
Fibrinogen, mg/dL	0.060	.137	0.052	.198
Homocysteine, μmol/L	0.011	.791	−.018	.661
Lp(a), mg/dL	−0.035	.391	−0.039	.340
SAA, μg/mL	0.106	.009	0.100	.014

Triglyceride, CRP, and Lp(a) were logarithmically transformed before statistical analysis to adhere to a normality assumption.

Table 3
The sICAM-1 levels according to the cardiovascular risk factors

		sICAM-1 levels (n)	*P*1[a]	*P*2[b]
Smoker	Noncurrent	232.3 ± 96.7 (493)		
	Current	267.0 ± 110.8 (116)	.001	<.001
Hypertension	Without	236.4 ± 101.2 (490)		
	With	249.4 ± 96.7 (119)	.205	.395
Diabetes mellitus	Nil	236.9 ± 99.5 (593)		
	Yes	313.2 ± 106.7 (16)	.003	.004
Obesity	Nil	234.4 ± 105.7 (367)		
	Yes	245.8 ± 91.5 (242)	.169	.288
Insulin resistance	Nil	229.3 ± 92.3 (457)		
	Yes	267.8 ± 117.2 (152)	<.001	<.001
Metabolic syndrome	Nil	230.8 ± 98.2 (497)		
	Yes	274.9 ± 102.3 (112)	<.001	<.001

[a] Not adjusted.
[b] Multiple linear regression adjusted for age and sex.

2.4. Statistical analysis

Spearman correlation coefficients were calculated to determine the association between sICAM-1 levels and measured cardiovascular risk factors. The χ^2 test or χ^2 test for trend examined statistical differences in the distribution of categorical data. The clinical characteristics of the continuous variables were expressed as mean ± SD and were tested by 2-sample *t* test or analysis of variance. Stepwise linear regression analysis was used to determine independent predictors of sICAM-1 levels. Because the distribution of triglyceride, CRP, and Lp(a) levels was skewed to the right, these values were logarithmically transformed before statistical analysis to adhere to a normality assumption. A *P* value less than .05 using a 2-sided test was considered statistically significant.

3. Results

3.1. Subject characteristics

A summary of demographic features, clinical and lipid profiles, and emerging cardiovascular risk factors for the study participants stratified by sex is provided in Table 1. No statistically significant differences in total cholesterol concentrations, LDL cholesterol levels, systolic BP, fibrinogen levels, Lp(a) levels, CRP levels, SAA levels, and sICAM-1 levels were observed between the sexes. Furthermore, the analysis showed that many variables were statistically significantly different between men and women. Compared

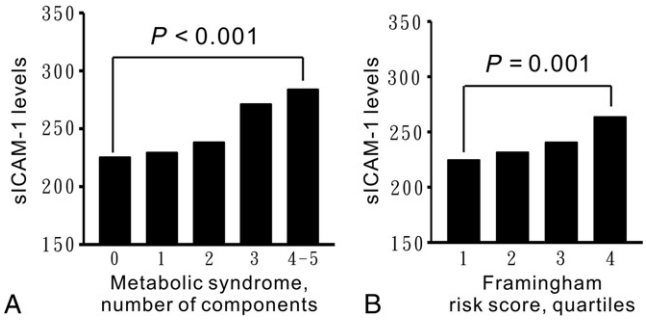

Fig. 1. Age- and sex-adjusted concentration of sICAM-1 according to the number of metabolic syndrome components and Framingham risk score quartiles for subjects without prevalent cardiovascular disease. The relationships between the number of metabolic syndrome components and sICAM-1 levels and between the risk score and sICAM-1 levels were significant by test-for-trends analysis ($P < .001$ and $P = .001$, respectively).

with women, significantly higher percentages of men were current smokers ($P < .001$) and obese ($P < .001$). Diastolic BP ($P < .001$), mean BP ($P < .001$), fasting plasma glucose ($P = .006$), fasting serum insulin ($P = .001$), HOMA index ($P < .001$), triglyceride levels ($P < .001$), BMI ($P < .001$), waist circumferences ($P < .001$), waist-hip ratio ($P < .001$), and homocysteine levels ($P < .001$) were statistically significantly higher in men than in women. In contrast, age ($P = .031$) and HDL cholesterol levels ($P < .001$) were lower in the men.

3.2. sICAM-1 and cardiovascular risk factors

Unadjusted and age- and sex-adjusted correlation coefficients between sICAM-1 levels and measured cardiovascular risk factors are shown in Table 2. There were significant positive associations of sICAM-1 levels with triglyceride levels, systolic BP, diastolic BP, mean BP, BMI, waist circumference, waist-hip ratio, fasting serum insulin, SAA levels, high-sensitivity CRP levels, and the HOMA index. There was a significant negative association between sICAM-1 levels and HDL cholesterol levels. Adjustment for age and sex did not substantially alter these correlations.

Table 3 shows the association between sICAM-1 levels and the presence or absence of several cardiovascular risk factors. After age and sex adjustment, serum concentrations of sICAM-1 were significantly higher in current smokers ($P = .001$). Significantly higher sICAM-1 levels were also noted in subjects with diabetes mellitus ($P = .004$), insulin resistance ($P < .001$), and metabolic syndrome ($P < .001$). The sICAM-1 levels increased in a stepwise fashion with increasing number of metabolic syndrome components ($P < .001$) as well as with increasing Framingham risk score quartiles ($P = .001$) (Fig. 1). In subjects with metabolic syndrome, sICAM-1 levels also increased with increasing CRP levels (age- and sex-adjusted Spearman rank coefficient, $\rho = 0.283$; $P = .003$).

In stepwise linear regression analysis in a model including age, sex, BMI, waist circumference, smoking, systolic and diastolic BP, serum triglyceride, HDL cholesterol, CRP, fibrinogen, homocysteine, Lp(a), SAA levels, insulin resistance, metabolic syndrome, and taking antihypertensive drugs, lipid-lowering drugs, or antidiabetic agents, current smoking ($P = .007$), insulin resistance ($P = .004$), and metabolic syndrome ($P = .008$) were significantly associated with elevated levels of sICAM-1.

4. Discussion

In this study, we demonstrated that elevated sICAM-1 levels were independently associated with insulin resistance, a marker of metabolic syndrome. We also showed that elevated sICAM-1 levels were associated with components of metabolic syndrome in age- and sex-adjusted models. Furthermore, sICAM-1 levels increased in a stepwise fashion with increasing components of metabolic syndrome; in subjects with metabolic syndrome, sICAM-1 levels increased with increasing CRP level. Thus, the present investigation provides further evidence of the association between elevated sICAM-1 levels, inflammation, and metabolic syndrome.

Several cardiovascular risk factors have been consistently associated with elevated sICAM-1 levels. Cigarette smoking has been associated with increased concentrations of sICAM-1 levels in a number of studies [14,16,18]. It has been shown that cigarette smoking can induce leukocyte-endothelial adhesion, microvascular and macrovascular entrapment of leukocytes, and leukocytes aggregation in human subjects and in animal models [22,23]. This is consistent with the present observation of a substantially higher concentration of sICAM-1 in current smokers. Inflammatory markers, including tumor necrotic factor–α, interleukin-6, and fibrinogen, have been shown to be determinants of adhesive molecular concentrations [13,14]. C-reactive protein has also been shown to be a positive determinant of sICAM-1 concentration [13,18,24]. Recent in vitro studies using human vascular endothelial cells demonstrated that CRP increased ICAM-1 expression in a dose-dependent manner, possibly through the complement as an intermediate [25]. Our data also showed that CRP plays an important role in determining sICAM-1 levels, supporting the association between sICAM-1 levels and inflammatory markers in the Taiwanese.

In contrast, there were controversial results regarding the association between hypertension or dyslipidemia and sICAM-1 levels. In the present study, using age- and sex-adjusted models, triglyceride levels were positively associated with sICAM-1 levels, whereas HDL cholesterol levels were negatively associated with them. This observation is in line with the concept (derived from experimental studies) that lipid metabolism modulates the expression of adhesive molecules [26]. This concept is supported by epidemiologic studies that showed association of sICAM-1 levels and lipid variables [16,18], although results have not been always

consistent in multivariate analysis [7,14]. The present data showed significant trends of high sICAM-1 levels with high BP in age- and sex-adjusted models, but not in multivariate analysis. Using multivariate analysis, Rohde et al [14] showed an independent association between systolic BP and sICAM-1 levels, whereas this was not replicated in other studies [16,23].

Plasma concentration of inflammatory mediators, such as tumor necrotic factor–α and interleukin-6, is increased in the insulin-resistant states of obesity and type 2 diabetes mellitus, raising questions about the mechanisms underlying inflammation in these 2 conditions [27,28]. Dandona et al [27] suggested that glucose and macronutrient intake causes oxidative stress and inflammatory changes that may interfere with insulin action by suppressing insulin signal transduction, resulting in insulin resistance. Previous epidemiologic studies have shown that elevated sICAM-1 levels are integral parts of insulin resistance in nondiabetic elderly persons but not in type 2 diabetes mellitus patients [15,29,30]. Circulating sICAM-1 concentrations were suggested to share common genetic modulation with traits related to obesity, insulin resistance, and HDL_3 cholesterol levels [17,31]. Our data revealed an independent association between sICAM-1 levels and insulin resistance and metabolic syndrome in a relatively young Taiwanese population. These results suggested that measurement of the inflammatory status, including sICAM-1 levels, may be a useful additional clinical indicator of insulin resistance and metabolic syndrome.

Combination of multiple risk factors seems to be a more powerful tool in predicting the risk of future cardiovascular events. Previous studies have shown a cumulative impact of multiple risk factors on sICAM-1 plasma concentration by using major risk factors and Framingham risk scores [14,16,18]. Metabolic syndrome is a constellation of multiple risk factors; growing evidence has shown an increased cardiovascular risk in individuals with metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III included "prothrombotic and proinflammatory states" as components of the metabolic syndrome, although these are not part of the clinical definition. Measurements of CRP also added clinically important prognostic information to the metabolic syndrome in a prospective study [32]. In the present investigation, sICAM-1 levels increased in a stepwise fashion with an increased number of components of metabolic syndrome, as well as with increased Framingham risk score quartiles. In subjects with metabolic syndrome, sICAM-1 levels also increased with increasing CRP levels. To the best of our knowledge, this is the first report showing an independent association between elevated sICAM-1 levels and metabolic syndrome with or without additional risk factors. However, the limitation of this study is its cross-sectional design because it provided no information about the effect of the sICAM-1 levels on the progression of insulin resistance/metabolic syndrome or clinical outcome.

In conclusion, using a combination of traditional and emerging risk factors with Framingham risk scores and with components of the metabolic syndrome, we showed that sICAM levels increase with an increasing risk of coronary artery disease. This finding supports the concept that this marker may be useful in predicting those at risk of future cardiovascular events. These data also provide further evidence of the mechanisms of sICAM-1 as a molecular marker for atherosclerosis. Further prospective studies will be necessary to clarify whether sICAM-1 level is an independent predictor of future atherosclerotic cardiovascular events.

Acknowledgment

This study was supported by a grant from Chang Gung Memorial Hospital (CMRPG 32098) to L-A Hsu, a grant from the National Science Council (NSC96-2314-B-303-012), and a grant from Tzu Chi University (TCIRP 95007) to Y-L Ko.

References

[1] Nicholls ES, Peruga A, Restrepo HE. Cardiovascular disease mortality in the Americas. World Health Stat Q 1993;46:134-50.
[2] Department of Health, Executive Yuan. Health and vital statistics II of the Republic of China, 1998; 1998. Taipei (Republic of China).
[3] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-26.
[4] Hansson GK. Immune mechanisms in atherosclerosis. Arterioscler Thromb Vasc Biol 2001;21:1876-90.
[5] Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. Atherosclerosis 2003;170:191-203.
[6] Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27:2292-301.
[7] Hwang SJ, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto Jr AM, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation 1997;96:4219-25.
[8] Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998;351:88-92.
[9] Becker A, van Hinsbergh VW, Jager A, Kostense PJ, Dekker JM, Nijpels G, et al. Why is soluble intercellular adhesion molecule–1 related to cardiovascular mortality? Eur J Clin Invest 2002;32:1-8.
[10] Witkowska AM, Borawska MH. Soluble intercellular adhesion molecule–1 (sICAM-1): an overview. Eur Cytokine Netw 2004;15:91-8.
[11] Malik I, Danesh J, Whincup P, Bhatia V, Papacosta O, Walker M, et al. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. Lancet 2001;358:971-6.
[12] Van der Meer IM, de Maat MP, Bots ML, Breteler MM, Meijer J, Kiliaan AJ, et al. Inflammatory mediators and cell adhesion molecules as indicators of severity of atherosclerosis: the Rotterdam Study. Arterioscler Thromb Vasc Biol 2002;22:838-42.
[13] Shai I, Pischon T, Hu FB, Ascherio A, Rifai N, Rimm EB. Soluble intercellular adhesion molecules, soluble vascular cell adhesion molecules, and risk of coronary heart disease. Obesity 2006;14:2099-106.
[14] Rohde LE, Hennekens CH, Ridker PM. Cross-sectional study of soluble intercellular adhesion molecule–1 and cardiovascular risk factors in apparently healthy men. Arterioscler Thromb Vasc Biol 1999;19:1595-9.

[15] Hak AE, Pols HA, Stehouwer CD, Meijer J, Kiliaan AJ, Hofman A, et al. Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: the Rotterdam study. J Clin Endocrinol Metab 2001;86:4398-405.

[16] Keaney Jr JF, Massaro JM, Larson MG, Vasan RS, Wilson PW, Lipinska I, et al. Heritability and correlates of intercellular adhesion molecule–1 in the Framingham Offspring Study. J Am Coll Cardiol 2004;44:168-73.

[17] Lee M, Czerwinski SA, Choh AC, Demerath EW, Sun SS, Chumlea WC, et al. Quantitative genetic analysis of cellular adhesion molecules: the Fels Longitudinal Study. Atherosclerosis 2006;185:150-8.

[18] Thorand B, Baumert J, Döring A, Schneider A, Chambless L, Löwel H, et al. Association of cardiovascular risk factors with markers of endothelial dysfunction in middle-aged men and women. Results from the MONICA/KORA Augsburg Study. Thromb Haemost 2006;95: 134-41.

[19] Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care 2004;27:1182-6.

[20] Chang PY, Wu TL, Tsao KC, Li CC, Sun CF, Wu JT. Microplate ELISAs for soluble VCAM-1 and ICAM-1. Ann Clin Lab Sci 2005;35: 312-7.

[21] Wu TL, Chen Tsai I, Chang PY, Tsao KC, Sun CF, Wu LL, et al. Establishment of an in-house ELISA and the reference range for serum amyloid A (SAA): complementarity between SAA and C-reactive protein as markers of inflammation. Clin Chim Acta 2007;376:72-6.

[22] MacNee W, Wiggs B, Belzberg AS, Hogg JC. The effect of cigarette smoking on neutrophil kinetics in human lungs. N Engl J Med 1989; 321:924-8.

[23] Bosken CH, Hards J, Gatter K, Hogg JC. Characterization of the inflammatory reaction in the peripheral airways of cigarette smokers using immunocytochemistry. Am Rev Respir Dis 1992;145:911-7.

[24] Ponthieux A, Herbeth B, Droesch S, Haddy N, Lambert D, Visvikis S. Biological determinants of serum ICAM-1, E-selectin, P-selectin and L-selectin levels in healthy subjects: the Stanislas study. Atherosclerosis 2004;172:299-308.

[25] Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000;102: 2165-8.

[26] Cockerill GW, Rye KA, Gamble JR, et al. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 1995;15:1987-94.

[27] Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004;25:4-7.

[28] Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448-54.

[29] Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S. Serum concentrations of soluble adhesion molecules are related to degree of hyperglycemia and insulin resistance in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2002;55:131-8.

[30] Leinonen E, Hurt-Camejo E, Wiklund O, Hultén LM, Hiukka A, Taskinen MR. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis 2003;166:387-94.

[31] Kent Jr JW, Comuzzie AG, Mahaney MC, Almasy L, Rainwater DL, VandeBerg JL, et al. Intercellular adhesion molecule–1 concentration is genetically correlated with insulin resistance, obesity, and HDL concentration in Mexican Americans. Diabetes 2004;53:2691-5.

[32] 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.