Letters

Clustering of Inflammatory Biomarkers and Risk of Hypertension in a Mongolian Population in China*

ZHU Xiao Hong[1,2], JIAO Yang[1], LI Hong Mei[1], WANG Ai Li[1], WANG Gui Yan[1,3], TONG Wei Jun[1], and ZHANG Yong Hong[1,#]

1. Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou 215123, Jiangsu, China; 2. Suzhou Industrial Park Centers for Disease Control and Prevention (Institute of Health Inspection and Supervision), Suzhou 215021, Jiangsu, China; 3. Department of Health Care, Xiamen Maternal and Child Care Hospital, Xiamen 361000, Fujian, China

Abstract

Objective There is little knowledge on whether there is clustering of inflammatory biomarkers, such as C-reactive protein (CRP), soluble intracellular adhesion molecule1-1 (sICAM-1), and angiotensin II (Ang II), in individuals with hypertension in the Mongolian population. In the present study, we investigated this relationship in a Mongolian population in China.

Methods A total of 2589 adult Mongolians, aged 20 years and older, were recruited as study participants. Data on demographics, lifestyle, family history of hypertension, blood pressure, and blood chemistry were collected, and inflammatory biomarkers were measured in all participants.

Results The proportion of subjects with increased levels of two or three biomarkers was significantly higher in those with hypertension (21.0% and 6.0%, respectively) than in those with prehypertension (12.7% and 0.5%, respectively) or normotension (8.1% and 0.2%, respectively). The multivariate adjusted odds ratios (95% confidence interval) of hypertension associated with increased levels of one, two or three biomarkers were 0.94 (0.72-1.22), 1.42 (0.93-2.16), and 11.08 (1.45-84.80), respectively, compared with subjects with no increase in any biomarker.

Conclusion Hypertension was associated with a cluster of inflammatory biomarkers in the Mongolian population.

Key words: C-reactive protein; Soluble intracellular adhesion molecule-1; Angiotensin II; Hypertension; Mongolia

Biomed Environ Sci, 2012; 25(5):562-568 *doi: 10.3967/0895-3988.2012.05.010* *ISSN:0895-3988*

www.besjournal.com(full text) *CN: 11-2816/Q*

INTRODUCTION

Hypertensive individuals are more likely to have a clustering of cardiovascular risk factors, such as obesity, diabetes, hyperlipidemia, than normotensive individuals[1-2]. Coexistence of hypertension and a cluster of cardiovascular risk factors is associated with an increased risk of cardiovascular disease and stroke[3-5]. In addition to the traditional cardiovascular risk factors, some biomarkers are associated with hypertension[6-7]. Inflammation and

*This study was supported by the National Natural Science Foundation of China (Grant No. 30972531) and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions.

#Correspondence should be addressed to: Professor ZHANG Yong Hong, PhD. Tel: 86-512-65880078, E-mail: yhzhang@suda.edu.cn

Biographical note of the first author: ZHU Xiao Hong, female, born in 1982, Ph. D candidate, majoring in epidemiology of cardiovascular disease.

Received: September 1, 2011; Accepted: April 3, 2012

endothelial dysfunction have been established as risk factors for atherosclerosis and clinical cardiovascular disease[8-10]. C-reactive protein (CRP) and soluble intracellular adhesion molecule-1 (sICAM-1) are important biomarkers produced in inflammation and endothelial dysfunction[10-11]. Apart from its role as a vasoconstrictor, angiotensin II (Ang II) also induces endothelial dysfunction and inflammation resulting in accelerated progression of atherosclerosis[12-13].

Previous studies[14-19] reported that an increased serum CRP level was associated with the risk of hypertension. There are also a few clinical studies[20-22] with small samples that indicated that increased circulating sICAM-1 was associated with hypertension. However, as far as we are aware, there are no reports about the relationship between a cluster of inflammatory biomarkers, including CRP, sICAM-1, and Ang II, and hypertension. In the present study, we examined the association between clusters of these factors and the risk of hypertension in a Mongolian population in China.

SUBJECTS AND METHODS

Study Participants

We conducted a cross-sectional study between 2002 and 2003 in Inner Mongolia, an autonomous region in China. The detailed methods for study participant selection and data collection were presented previously[23]. Briefly, study participants, aged 20 years and older, were recruited from 32 villages in two adjacent townships located in Kezuohou Banner (county) and Naiman Banner in Inner Mongolia. The majority of local residents were Mongolians who had lived there for many generations and maintained a traditional diet and lifestyle. The study population consisted of both farmers and herdsmen whose diets were high in fat and salt. There were a total of 3 475 Mongolian subjects aged 20 years and older living in these villages; among them, 2 589 unrelated subjects participated in the study. None of the participants had chronic kidney disease, malignant tumor, thyroid disease or adrenalopathy associated with secondary hypertension, or acute infectious disease. This study was approved by the Soochow University Institutional Review Board. Written informed consent was obtained for all study participants.

Data Collection

Data on demographics, lifestyle risk factors, family history of hypertension and personal medical history were obtained using a standard questionnaire administered by trained staff. Cigarette smoking was defined as having smoked at least one cigarette per day for 1 year or more. The amount and type of alcohol consumed during the past year was determined, and alcohol drinking was defined as consuming at least 50 g alcohol per day for 1 year or more.

Three sitting blood pressure (BP) measurements were taken by trained observers using a standard mercury sphygmomanometer according to a standard protocol, after the subjects had been resting for 30 min. The first and fifth Korotkoff sounds were recorded as systolic BP (SBP) and diastolic BP (DBP), respectively. The mean of the three BP measurements was used in the analysis. According to JNC7 of 2003 from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP, participants were stratified into three groups as follows: (1) normotension: SBP <120 mmHg and DBP <80 mmHg without use of antihypertensive medication; (2) prehypertension: SBP 120-139 mmHg and/or DBP 80-89 mmHg without the use of antihypertensive medication; and (3) hypertension: SBP $\geqslant$140 mmHg and/or DBP $\geqslant$90 mmHg and/or use of antihypertensive medication in the last 2 weeks. Body weight and height were measured using standard methods and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was measured at the level of 1 cm above the umbilicus.

Blood samples were collected in the morning after at least 8 h of fasting. All plasma and serum samples were frozen at -80 °C until laboratory testing. Fasting plasma glucose (FPG) was examined using a glucose meter (Roche, Basel, Switzerland). Concentrations of total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides were assessed enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, CA, USA) using commercial reagents, and low density lipoprotein (LDL)-cholesterol was calculated by means of the Friedewald equation for participants who had less than 400 mg/dL triglycerides[24]. CRP was determined by an immunoturbidimetric assay on a Beckman Synchron CX5 Delta Clinical System using commercial reagents. sICAM-1 was measured by an ELISA assay (R&D Systems, Minneapolis, MN, USA) which employs the quantitative sandwich

enzyme immunoassay technique. Ang II concentration was measured by radioimmunoassay after separation by high performance liquid chromatography.

Statistical Analysis

The age-and gender-standardized rate of categorical variables for baseline characteristics was calculated by using a direct standardization method with the study population as reference for hypertensive, prehypertensive and normotensive groups. Groups were compared using the X^2 test. For continuous variables that were not normally distributed, the age- and gender-adjusted median and interquartile range were presented according to hypertension status and *P*-values were determined with the Kruskal-Wallis H test for the difference in medians. The age- and gender-adjusted mean was calculated according to hypertension status for the continuous variables found to be normally distributed, and analysis of covariance was used to calculate the *P*-value for the difference in the means. All participants were divided evenly into four groups according to quartiles of CRP, sICAM-1, and Ang II. Increased CRP, sICAM-1, and Ang II levels were defined as those in the highest quartiles. The rates of increased CRP, sICAM-1, and Ang II were calculated in normotensive, prehypertensive and hypertensive groups, and compared between groups. The prevalence of clusters of increased levels of the inflammatory biomarkers was calculated for normotensive, prehypertensive and hypertensive groups. Trend tests for rates and constituent ratios were conducted using the Cochrane-Armitage trend test and Cochrane-Mantel-Haenszel test. Multiple logistic regression analysis (proportional odds model) was used to analyze the association between clusters of inflammatory biomarkers and hypertension and prehypertension. All *P*-values were two-tailed and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 2 589 participants, 1 064 male and 1 525 female, aged 20-84 years (mean 46.5 years), was included in this analysis. There were 968 participants with hypertension, 994 participants with prehypertension, and 627 participants with normotension. A comparison of the baseline characteristics among normotensive, prehypertensive and hypertensive is presented in Table 1.

Table 1. Comparison of Baseline Characteristics between Normotensive, Prehypertensive, and Hypertensive Groups

Variables	Normotension (*n*=627)	Prehypertension (*n*=994)	Hypertension (*n*=968)
Age, mean (SD), year	41±11	45±12†	52±12†‡
Male, %	27.11	41.15†	50.10†‡
Family history of hypertension, %	3.83	7.55†	24.69†‡
Alcohol drinking, %	20.10	31.29†	44.32†‡
Smoking, %	40.99	43.06	48.24†
BMI, median (IQR), kg/m^2	20.9 (19.3, 23.0)	21.5 (19.8, 23.7)†	22.6 (20.2, 25.7)†‡
Waist, median (IQR), cm	76 (72,82)	79 (74, 85)†	83 (77, 90)†‡
Heart rate, median (IQR), beat/min	72 (68, 80)	74 (68, 82)	76 (70, 82)†‡
Triglycerides, median (IQR), mmol/L	0.80 (0.55, 1.44)	0.92 (0.65, 1.35)†	1.12 (0.78, 1.77)†‡
Total cholesterol, median (IQR), mmol/L	3.34 (2.80, 3.96)	3.56 (2.94, 4.29)†	3.80 (3.10, 4.68)†‡
LDL- cholesterol, mean (SD), mmol/L	2.10 (0.91)	2.27 (1.00)†	2.49 (1.10)†‡
HDL-cholesterol, mean (SD), mmol/L	1.16 (0.31)	1.18 (0.34)	1.17 (0.33)
FPG, median (IQR), mmol/L	4.60 (4.10, 5.20)	4.80 (4.30, 5.40)†	5.10 (4.50, 5.70)†‡
Ang II, median (IQR), pg/mL	47.75 (38.60, 65.90)	47.00 (40.00, 67.20)	52.00 (40.50, 83.80)†‡
CRP, median (IQR), mg/L	4.85 (3.30, 8.14)	5.86 (3.85, 10.75)†	7.43 (4.57, 10.07)†‡
sICAM-1, mean (SD), ng/mL	314.140 (93.67)	328.05 (98.22)†	339.16 (99.13)†‡

Note. IQR: interquartile range; SD: standard deviation; BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; FPG: fasting plasma glucose; Ang II: Angiotensin II; CRP: C-reactive protein; sICAM-1: soluble intracellular adhesion molecule-1. $^{\dagger}P<0.05$ compared with normotension; $^{\ddagger}P<0.05$ compared with prehypertension.

The participants with prehypertension were more likely to be older and male, to have higher rates of a family history of hypertension and alcohol drinking, and higher BMI, WC, TG, TC, LDL-C, FPG, CRP, and sICAM-1 compared with normotensives (all $P<0.05$). Participants with hypertension were more likely to be older and male, to have higher rates of a family history of hypertension and alcohol drinking, and higher BMI, WC, TG, TC, LDL-C, FPG, CRP, sICAM-1, and Ang II compared with those with prehypertension (all $P<0.05$).

In the three groups, the proportion of participants with increased CRP, ICAM-1 and Ang II and the proportion with zero, one, two, or three increased biomarkers are listed in Table 2. The proportions of participants with increased CRP and increased sICAM-1 were significantly higher in those with prehypertension than in those with normotension ($P<0.05$). The proportions of participants with increased CRP, sICAM-1 and Ang II in the hypertensive group were also significantly higher than in the prehypertensive and normotensive groups ($P<0.05$). There was a trend for the proportion of those with a cluster of 2 or 3 biomarkers increase from normotension to prehypertension to hypertension ($P<0.001$).

With normotensives as controls, the unadjusted odds ratio (OR) and 95% confidence interval (95% CI) for prehypertension and hypertension associated with the number of biomarkers with increased levels are listed in Table 3. The unadjusted ORs for prehypertension for one or two biomarkers were significant, and the OR for a cluster of three biomarkers was not significant. However, in multivariate analysis, adjusted ORs for prehypertension for one, two, or three biomarkers were not significant. There was a significant association between the clusters of biomarkers and hypertension. The unadjusted ORs of hypertension associated with one, two, or three biomarkers were all significant compared with subjects with no increased biomarker. After adjustment in the multivariate analysis, only the OR for hypertension for a cluster of three biomarkers remained significant, with the risk of hypertension 11-fold higher than in those without increased biomarkers.

Table 2. Proportions of Increased Levels of Biomarkers and Numbers of Increased Biomarkers among Normotensive, Prehypertensive, and Hypertensive Groups

Groups	Increased CRP *n* (%)	Increased sICAM-1 *n* (%)	Increased Ang II *n* (%)	Numbers of Increased Biomarkers			
				0, %	1, %	2, %	3, %
Normotension	93 (14.9)	119 (19.0)	127 (20.3)	52.9	38.9	8.1	0.2
Prehypertension	238 (23.9)†	241 (24.3)†	224 (22.5)	41.7	44.8	12.7	0.8
Hypertension	315 (32.6)†‡	287 (29.7)†‡	297 (30.7)†‡	37.6	35.4	21.0†‡	6.0†‡
Trend test χ^2	63.68	21.99	23.9	95.24			
P-value	<0.001	<0.001	<0.001	<0.001			

Note. †$P<0.05$ compared with normotension; ‡$P<0.05$ compared with prehypertension.

Table 3. Odds Ratios (95% Confidence Interval) for Prehypertension and Hypertension According to Number of Biomarkers with Increased Levels

Number of Biomarkers Increased	Prehypertension				Hypertension			
	Unadjusted	*P*	Multivariate Adjusted*	*P*	Unadjusted	*P*	Multivariate Adjusted*	*P*
0	1.00		1.00		1.00		1.00	
1	1.45 (1.13-1.80)	0.002	1.20 (1.01-1.68)	0.04	1.22 (1.01-1.60)	0.03	0.98 (0.68-1.22)	0.545
2	1.92 (1.33-2.80)	<0.001	1.32 (0.92-2.07)	0.133	3.61 (2.37-5.28)	<0.001	1.46 (0.97-2.16)	0.08
3	5.72 (0.62-46.08)	0.112	2.46 (0.69-19.34)	0.15	43.21 (6.31-350.82)	<0.001	11.02 (1.46-83.82)	0.006

Note. *Adjusted for age, sex, family history of hypertension, smoking, alcohol drinking, heart rate, BMI, waist circumference, fasting plasma glucose, triglycerides, total cholesterol, and HDL-cholesterol.

DISCUSSION

Our study showed that the levels of CRP and sICAM-1 were significantly higher in participants with prehypertension than in those with normotension. The levels of all three biomarkers were significantly higher in participants with hypertension than in those with prehypertension or normotension. There was a phenomenon of clustering of biomarkers with increased levels in hypertension. The proportion of two or three biomarkers was higher in hypertension than in both prehypertension and normotension. These findings imply that increased levels of biomarkers, especially a cluster of biomarkers, could play a role in the development of hypertension.

Some studies have reported that a single biomarker is associated with hypertension. Bautista[15], Sung[16], and Lakoski[17] reported that CRP might be an independent risk factor of hypertension. Cottone et al.[22] reported that clinical hypertension patients showed higher levels of sICAM-1 than healthy controls. Ang II may play a direct role in inducing hypertension by increasing oxidative stress and inflammation[25]. Recently, a cross-sectional study in a Korean population showed that the prevalence of hypertension was 1.27, 1.25, and 1.45 times higher in patients in the second, third, and fourth quartiles of CRP after multivariate adjustment, compared to those in the lowest quartile[16]. Similarly, Ridker et al.[10] reported a higher risk of hypertension associated with increased CRP, and showed that the relative risks were 2.1, 2.1, and 4.4 for women in the second, third, and fourth quartiles, respectively, compared with those in the lowest quartile of CRP. A follow-up study by Sesso[19] indicated that high CRP levels in serum were associated with a 1.5-fold increase in risk of hypertension in females aged 45 years or older. In addition, apart from the association between increased CRP and hypertension, increased CRP was also associated with prehypertension. For example, Chrysohoou et al.[26] reported that 31% of participants with prehypertension had increased CRP in the ATTICA study, indicating that the inflammatory process had already been initiated in the prehypertensive stage.

A few clinical studies provided evidence that increased circulating adhesion molecules were also associated with hypertension[20-22]. DeSouza and colleagues[20] reported that 11 hypertensive patients had significantly higher plasma levels of sICAM-1 compared with 10 normotensive controls. Hlubocka et al.[21] found that 22 hypertensive patients had significantly higher levels of sICAM-1 compared with 22 normotensive controls. Cottone et al.[22] reported that 216 hypertensive patients showed higher levels of sICAM-1 than 55 healthy controls. In our large population-based study, plasma levels of sICAM-1 were significantly higher in hypertension compared with both prehypertension and normotension, and plasma levels of sICAM-1 were significantly higher in prehypertension compared with normotension. Apart from its role as a vasoconstrictor, Ang II also induces endothelial dysfunction and inflammation resulting in accelerated progression of atherosclerosis[12-13]. Recently, Liao et al conducted an animal experiment using CC chemokine receptor 2-knockout mice to examine the association between Ang II-induced hypertension and oxidative stress or inflammation, and concluded that in Ang II-induced hypertension, CC chemokine receptor 2 activation plays an important role in the development of hypertension via increased oxidative stress and inflammation[25].

The biomarkers CRP, ICAM-1, and Ang II may be mutually related to each other in the mechanism of development of hypertension. A study showed CRP independently upregulates Ang II type-1 receptors, which could result in subsequent elevation of BP[27]. Additionally, CRP inhibits endothelial nitric oxide synthase and upregulates adhesion molecules (sICAM, vascular cell adhesion molecule, and E-selectin) and promotes increased monocyte adhesion[11]. Ang II also upregulates ICAM-1 expression and stimulates *in vitro* and *in vivo* sICAM-1 release[13,28].

There are also some studies to suggest that CRP may play a direct role as a mediator in atherogenesis by inducing ICAM expression[9,29]. Plasma levels of CRP and adhesion molecules are related to the risk of cardiovascular disease and have direct clinical and public health implications[9-10,30].

Our findings indicate that the clustering of increased CRP, ICAM-1, and Ang II is mutually associated with hypertension, which further provides support that inflammation may play a role in the development of hypertension. However, although the association of clusters of increased CRP, ICAM-1, and Ang II with prehypertension did not reach a statistically significant level; this may be because the prehypertensive participants included a high proportion of individuals with SBP/DBP <130/85 mmHg, who are likely to have much lower levels of the biomarkers. It also must be noted that the 95%

CI of the OR for hypertension for clustering of three biomarkers is quite wide. In this logistic analysis, there were considerably fewer subjects with increased levels of all three biomarkers in hypertension (6%); therefore, the 95% CI of the OR for a cluster of three biomarkers was wide.

There are some limitations to this study. First, this was a cross-sectional study; therefore a causal relationship between inflammatory biomarkers and the risk of hypertension or prehypertension could not finally be established. Second, approximately 25% of the eligible population from these villages chose not to participate which might have introduced some selection bias. However, we believe this bias was minimal because it was unlikely that the reasons for not participating were related to their BP or biomarker levels, of which they were unaware. There are several important strengths of our study which deserve mention. This was a large study to examine the association between the clustering of inflammatory biomarkers and hypertension in an Asian population. The study participants were homogeneous regarding their genetic background and environmental exposures. The study data were collected with rigid quality control and important co-variables were measured and controlled in the analysis.

In conclusion, this study in a homogeneous Mongolian population, found that hypertension was associated with a cluster of inflammatory biomarkers, CRP, ICAM-1, and Ang II.

ACKNOWLEDGEMENTS

We are deeply appreciative of the participants in the study, and thank Kezuohouqi Banner Center for Disease Prevention and Control, and Naiman Banner Center for Disease Prevention and Control for their support and assistance.

REFERENCES

1. Nakanishi N, Suzuki K, Tatara K. Clustering of cardiovascular risk factors and risk of development of hypertension in Japanese male office workers. J Cardiovasc Risk, 2003; 10, 213-20.
2. Zhang M, Batu B, Tong W, et al. Prehypertension and Cardiovascular Risk Factor Clustering Among Mongolian Population in Rural and Animal Husbandry Area, Inner Mongolia, China. Circ J, 2009; 73, 1437-41.
3. Du X, McNamee R, Cruickshank K. Stroke risk from multiple risk factors combined with hypertension: a primary care based case-control study in a defined population of northwest England. Ann Epidemiol, 2000; 10, 380-8.
4. Smith SC. Multiple Risk Factors for Cardiovascular Disease and Diabetes Mellitus. Am J Med, 2007; 120 (3A), S3-S11.
5. Barreto SM, Passos VM, Firmo JOA, et al. Hypertension and clustering of cardiovascular risk factors in a community in Southeast Brazil–The Bambui health and ageing study. Arq Bras Cardiol, 2001; 77, 576-81.
6. Freestone B, Gustafsson F, Chong AY, et al. Influence of atrial fibrillation on plasma von willebrand factor, soluble E-selectin, and N-terminal pro B-type natriuretic peptide levels in systolic heart failure. Chest, 2008; 133, 1203-8.
7. Spencer CG, Felmeden DC, Blann AD, et al. Haemorheological, platelet and endothelial indices in relation to global measures of cardiovascular risk in hypertension patients: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. J Intern Med, 2007; 261, 82-90.
8. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol, 2008;103,398-406.
9. Szmitko PE, Wang CH, Weisel RD, et al. New markers of inflammation and endothelial cell activation, part I. Circulation, 2003; 108, 1917-23.
10. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Eng l J Med, 2000; 342, 836-43.
11. Bautista LE. Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. J Hum Hypertens, 2003, 17, 223-30.
12. Schiffrin EL, Touyz RM. Multiple actions of angiotensin II in hypertension: benefits of AT1 receptor blockade. J Am Coll Cardiol, 2003; 42, 911-3.
13. Pastore L, Tessitore A, Martinotti S, et al. Angiotensin II stimulates intercellular adhesion molecule-1 (ICAM-1) expression by human vascular endothelial cells and increases soluble ICAM-1 release *in vivo*. Circulation, 1999; 100, 1646-52.
14. Schillaci G, Pirro M, Gemelli F, et al. Increased C-reactive protein concentrations in never-treated hypertension: the role of systolic and pulse pressures. J Hypertens, 2003; 21, 1841-6.
15. Bautista LE, López-Jaramillo P, Vera LM, et al. Is C-reactive protein an independent risk factor for essential hypertension? J Hypertens, 2001; 19, 857-61.
16. Sung KC, Suh JY, Kim BS, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension. Am J Hypertens, 2003; 16, 429-33.
17. Lakoski SG, Herrington DM, Siscovick DM, et al. C-reactive protein concentration and incident hypertension in young adults: the CARDIA study. Arch Intern Med, 2006; 166, 345-9. Arch Intern Med, 2006; 166, 345-9.
18. Davey SG, Lawlor DA, Harbord R, et al. Association of C-reactive protein with blood pressure and hypertension life course confounding and Mendelian randomization tests of causality. Arterioscler Thromb Vasc Biol, 2005; 25, 1051-6.
19. Sesso HD, Buring JE, Rifai N, et al. C-reactive protein and the risk of developing hypertension. JAMA, 2003; 290, 2945-51.
20. DeSouza CA, Dengel DR, Macko RF, et al. Increased levels of circulating cell adhesion molecules in uncomplicated essential hypertension. Am J Hypertens, 1997; 10, 1335-41.
21. Hlubocka Z, Umnerova V, Heller S, et al. Circulating intercellular cell adhesion molecule-1, endothelin-1 and von

Willebrand factor-markers of endothelial dysfunction in uncomplicated essential hypertension: the effect of treatment with ACE inhibitors. J Human Hypertens, 2002; 16, 557-62.

22. Cottone S, Mule G, Nardi E, et al. C-reactive protein and intercellular adhesion molecule-1 are stronger predictors of oxidant stress than blood pressure in established hypertension. J Hypertens, 2007; 25, 423-8.
23. Li H, Xu T, Tong W, et al. Comparison of Cardiovascular Risk Factors Between Prehypertension and Hypertension in a Mongolian Population, Inner Mongolia, China. Circ J, 2008; 72, 1666-73.
24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18, 499-502.
25. Liao TD, Yang XP, Liu YH, et al. Role of inflammation in the development of renal damage and dysfunction in angiotensin II-induced hypertension. Hypertension, 2008; 52, 256-63.
26. Chrysohoou C, Pitsavos C, Panagiotakos DB, et al. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: The ATTICA Study. Am J Hypertens, 2004; 17, 568-73.
27. Wang CH, Li SH, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation, 2003; 107, 1783-90.
28. Liu HQ, Wei XB, Sun R, et al. Angiotensin II stimulates intercellular adhesion molecule-1 via an AT1 receptor/nuclear factor-kappaB pathway in brain microvascular endothelial cells. Life Sci, 2006; 78, 1293-8.
29. Pasceri V, Willerson JT, Yeh ETH. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation, 2000; 102, 2165-8.
30. Hwang SJ, Ballantyne CM, Sharrett AR, et al. Circulating adhesion molecules VCAM-a, ICAM-1, and E-selectin carotid atherosclerosis and incident coronary heart disease cases. Circulation, 1997; 96, 4219-25.