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The relationship between serum sialic acid and high-sensitivity C-reactive protein with prehypertension

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of our study was to evaluate the serum concentration of sialic acid (SA) and high-sensitivity C-reactive protein (hs-CRP) in prehypertensive patients and the possible correlations between these 2 factors with blood pressure in such patients.

Material/Methods: We studied 61 prehypertensive patients, 70 hypertensive patients, and 50 controls with normal blood pressure. Lipid profile, hs-CRP, SA, and body mass index (BMI) were estimated in all groups. Associations between SA and hs-CRP and blood pressure were analyzed using multiple linear regressions.

Results: SA and hs-CRP levels were higher in the prehypertension group than that in the control group and were lower than that in the hypertension group. Multiple linear regression demonstrated that fasting glucose, BMI, SA, and hs-CRP correlated with systolic blood pressure and that low-density lipoprotein, BMI, SA, and hs-CRP correlated independently with diastolic pressure ($P<0.05$).

Conclusions: Our findings suggest that in prehypertension, there is an association between serum SA and hs-CRP levels and blood pressure.

MeSH Keywords: Pre-Hypertensions • CMP Sialic Acid • Protein, C-Reactive

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Background

Hypertension is a major cardiovascular risk factor, and cardiovascular disease is a leading cause of premature morbidity and mortality in China [1,2]. The Joint National Committee 7 (JNC 7) report describes prehypertension as an independent category of blood pressure [3]. With the exception of people who take antihypertensive drugs, people with systolic blood pressure (SBP) between 120 and 139 mmHg or diastolic blood pressure (DBP) between 80 and 89 mmHg are deemed to have prehypertension. Compared to people with normal blood pressure, prehypertensive people are at twice the risk for developing hypertension [4]. These people require lifestyle modifications to decrease the risk of progression to hypertension and to prevent cardiovascular disease. In the clinical setting, elevation of serum factors such as low-density lipoprotein cholesterol (LDL) were believed to be predictive factors for atherosclerotic cardiovascular disease and mortality [5]. Besides these traditional risk factors, high-sensitivity C-reactive protein (hs-CRP), a marker of low-grade inflammation, has been used as a predictor of cardiovascular mortality and morbidity in healthy people [6]. Elevation of hs-CRP may suggest acute involvement of inflammation in the development of hypertension and always occurs before blood pressure elevation [7,8]. At the same time, it was demonstrated that elevated serum sialic acid (SA) is associated with increased cardiovascular mortality [9–11] and could be associated with prehypertension in Indians [12]. The purpose of this study was to investigate the correlations of SA and hs-CRP in Chinese prehypertensive patients. We detected and analyzed potential cardiovascular risk factors such as dyslipidemia, elevated hs-CRP, and SA to explore the possible relationship between these 2 factors in volunteers with hypertension, prehypertension, and normal blood pressure.

Material and Methods

The study protocol received ethics approval from the China-Japan Friendship Hospital Regional Ethics Committee. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

We enrolled 181 volunteers deemed healthy based on physical examination at the China-Japan Friendship Hospital in July 2011. Detailed history-taking and physical examination were carried out on these volunteers. We excluded volunteers with the following conditions: secondary hypertension, coronary heart disease, myocardial infarction, heart failure, cerebrovascular disease, diabetes, gout, incomplete liver and kidney function, recent infection, pregnancy, habitual drinking, habitual smoking, blood system diseases, and other endocrine diseases. Based on the 2010 China hypertension prevention and control guidelines, the volunteers were divided into 3 groups: 50 in the normal blood pressure group (control; SBP <120 mmHg, DBP <80 mmHg), 61 in the prehypertension group (SBP 120~139 mmHg and/or DBP 80~89 mmHg), and 70 in the hypertension group (SBP ≥140 mmHg and/or DBP 90 mmHg).

Blood pressure was determined using a standard mercury sphygmomanometer; it was measured thrice and the average value was recorded as the volunteer's blood pressure. The body mass index (BMI) was derived using the volunteers' weights and heights. Volunteers were required to eat lightly for 3 days before measurements were obtained, with a compulsory water-only fast 12 h before measurement; 5 mL venous blood was collected from the volunteers in resting conditions. The plasma was used for estimating the lipid profile, apolipoprotein B, serum hs-CRP, and SA. All indicators were detected using an automated Hitachi 7600 biochemical analyzer. Shanghai Shen SuoYou Fu Medical Diagnostic Products provided the reagents for testing serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), LDL, and fasting glucose (FBG). The Landau British company provided the reagents for hs-CRP and the serum SA detection kit was from Wenzhou East Ou Jin Ma Biotechnology.

All analyses were performed using SPSS 19.0 (CA). Variance analysis was used for comparison among groups and *t*-test was used for comparison between groups. The relationship between serum SA and hs-CRP with prehypertension was analyzed using multiple linear stepwise regression analysis. $P<0.05$ indicated a statistically significant difference and $P<0.01$ and $P<0.001$ indicated highly significant differences.

Results

Figure 1 depicts the general characteristics and clinical profiles of the hypertensive, prehypertensive, and control volunteers. There was no significant difference in sex and age among these 3 groups. There was a significant gradient increase in SBP, DBP, BMI, SA, and hs-CRP levels in all 3 groups. The levels of SA, hs-CRP, and BMI in prehypertensive patients were higher than in healthy controls (P=0.015,0.006, and 0.004, respectively; Figure 1A, 1B, 1E) and lower than in hypertensive groups (P=0.02, 0.008, 0.005, respectively; Figure 1A, 1B, 1E). The level of HDL in prehypertensive patients was lower than in healthy controls and higher than in hypertensive groups (P=0.007 and 0.004, respectively; Figure 1D).Compared with the controls, TC, LDL, and FBG levels were significantly increased in hypertensive volunteers (P=0.003, 0.008, 0.002; respectively, Figure 1C, 1D, 1F). There was no difference in TG among the 3 groups. There were no significant differences in TC, LDL, and FBG between healthy controls and prehypertensive patients or between prehypertensive and hypertensive patient groups. We used multiple linear

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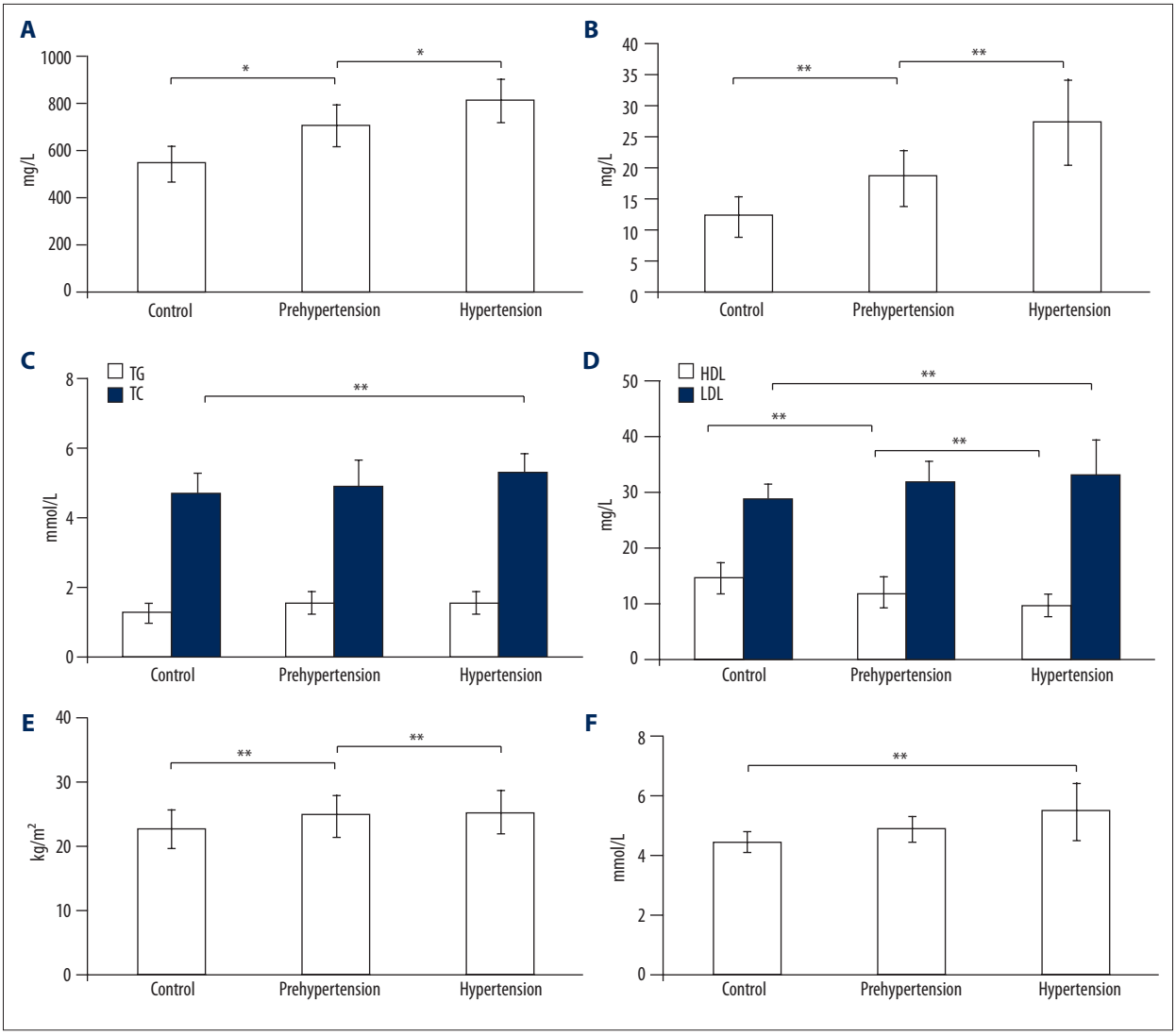

Figure 1. Study population characteristics and comparison of healthy controls with hypertensive and prehypertensive volunteers: sialic acid (SA), high-sensitivity C-reactive protein (hs-CRP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), body mass index (BMI), fasting glucose (FBG). (**A**) SA, (**B**) hs-CRP, (**C**) TG and TC, (**D**) HDL and LDL, (**E**) BMI, and (**F**) FBG.

stepwise regression to evaluate the relationship between serum SA and hs-CRP with blood pressure in the 3 groups. Using SBP and DBP as dependent variables and TC, HDL, LDL, TG, FBG, BMI, SA, and hs-CRP as independent variables, we found that FBG, BMI, SA, and hs-CRP were independently associated with SBP (P=0.02, 0.001, 0.01, 0.002, respectively; Table 1), and LDL, BMI, SA, and hs-CRP were independently associated with DBP (P=0.03, 0.03, 0.04, 0.001, respectively; Table 2).

Discussion

There is a positive correlation between hypertension and cardiovascular disease, and hypertension is becoming a serious threat to human health. The JNC 7 report describes prehypertension as an independent category of blood pressure [3]. Vasan et al. [4] demonstrated that prehypertension precedes the development of hypertension in 90% of people and that it can increase the risk of cardiovascular disease [13–17]. Identifying the risk factors for early hypertension would be of great significance in preventing cardiovascular disease [18].

CRP, which is synthesized by the liver [19], can respond to factors released by macrophages and fat cells [20]. As an acute-phase protein active in the response to inflammation, CRP also can predict cardiovascular mortality and morbidity in healthy people. In this study, hs-CRP levels were increased significantly in all 3 groups. There was a positive correlation between serum

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Table 1. Multiple linear regression analysis of variables and SBP.

Variable	B	Beta	t value	*P* value
Constant term	51.28		13.09	0.001
SA	0.06	0.29	2.64	0.01
Hs-CRP	4.67	0.36	3.16	0.002
BMI	2.47	0.17	3.64	0.001
FBG	6.68	0.14	2.37	0.02

SBP – systolic blood pressure; SA – sialic acid; hs-CRP – high-sensitivity C-reactive protein; BMI – body mass index; FBG – fasting glucose.

Table 2. Multiple linear regression analysis of variables and DBP.

Variable	B	Beta	t value	*P* value
Constant term	48.62		13.26	0.001
SA	0.04	0.21	2.11	0.04
Hs-CRP	3.24	0.22	3.39	0.001
BMI	1.71	0.15	2.18	0.03
LDL	3.63	0.19	2.19	0.03

DBP – diastolic blood pressure; SA – sialic acid; hs-CRP – high-sensitivity C-reactive protein; BMI – body mass index; LDL – low-density lipoprotein cholesterol.

hs-CRP level and SBP and DBP. This suggests that blood CRP may be a risk factor for progression of hypertension. The following facts may be associated with the relationship between serum CRP and blood pressure [21,22]: (1) CRP can damage vascular endothelial cells, reduce the release of nitric oxide and prostaglandin, and weaken the vasodilatation function; (2) Elevation of blood pressure can damage vascular endothelial cells and activate the inflammation response, followed by elevated CRP; and (3) Elevated CRP can increase endothelin release, contract blood vessels, and promote vascular smooth-muscle cell proliferation and migration, and the development of atherosclerosis. Overall, CRP is an important inflammatory factor, being significantly correlated with blood pressure in prehypertensive and hypertensive volunteers.

Widely distributed in mammalian cells, SA is particularly abundant in vascular endothelial cells. Several studies have demonstrated an association between serum SA and cardiovascular mortality in the general population [23,24]. As a potential risk factor, SA can be an acute-phase response marker in cardiovascular disease [25]. In this study, there was a significant gradient increase in the SA levels of prehypertensive and hypertensive volunteers compared with that of the controls ($P<0.05$). This suggests that the blood SA levels in these volunteers increased before they developed high blood pressure. In other words, SA level elevation strongly suggests the possibility of hypertension. Regression analysis showed that serum SA level was closely related with SBP and DBP. Three mechanisms may be involved in the influence of blood SA levels on blood pressure [26,27]. Firstly, SA can promote atherosclerosis development by the inflammatory response, interfere with iron metabolism, and promote platelet thrombus formation mechanisms. The development of atherosclerosis can promote hypertension indirectly. Secondly, SA is the main source of vascular endothelial cell surface negative charge; it can influence the vascular endothelial cell function for promoting the development of hypertension. Thirdly, SA can also affect LDL metabolism, inducing vascular smooth muscle damage, and the damaged muscle can promote the development of hypertension. Similar to CRP, SA is associated with and is a predictor of cardiovascular disease and type 2 diabetes [10,28]. Compared with CRP, SA may be a more stable inflammatory marker because it can reflect the overall level of acute-phase reaction, whereas CRP only represents the acute-phase reaction when it is released from the liver [12].

There were significant differences in TC, LDL, and FBG levels between the prehypertension and control groups. The increased TC and LDL levels suggested that the prehypertensive volunteers also had blood lipid and blood glucose disorders. These

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disorders also can promote the risk of high blood pressure and cardiovascular disease. Blood lipids, blood glucose, and blood pressure can be involved in synergistic mutual promotion.

Conclusions

In conclusion, acute-phase markers such as SA and hs-CRP were significantly increased in prehypertensive and hypertensive volunteers. The increased serum SA and hs-CRP levels were independently associated with SBP and DBP, respectively. Higher levels of these 2 factors may suggest a greater risk for future high blood pressure. Clinically, comprehensive hypertension risk can be evaluated by detecting blood, salivary, and serum CRP in prehypertensive patients, and pharmacological tools can be developed to ameliorate the development of hypertension in this highly susceptible section of the population.

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