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Blood Pressure Increase and Incidence of Hypertension in Relation to Inflammation-Sensitive Plasma Proteins

Gunnar Engström, Lars Janzon, Göran Berglund, Peter Lind, Lars Stavenow, Bo Hedblad, Folke Lindgärde

Objective—The reasons for the relationship between inflammation-sensitive plasma proteins (ISPs) and incidence of cardiovascular diseases are poorly understood. This study explored the hypothesis that ISPs are associated with future hypertension and age-related blood pressure increase.

Method and Results—Blood pressure and plasma levels of fibrinogen, α 1-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid were determined in 2262 healthy men aged 35 to 50 years, initially without treatment for hypertension. The cohort was re-examined after 15.7 (\pm 2.2) years. Incidence of hypertension and blood pressure increase was studied in relation to number of elevated proteins (ie, in the top quartile) at baseline. Among men without treatment for hypertension at follow-up, mean (\pm SD) increase in systolic blood pressure was 18.8 \pm 17, 19.2 \pm 17, 19.3 \pm 17, and 22.1 \pm 18 mm Hg, respectively, for men with 0, 1, 2, and \geq 3 elevated proteins (P for trend=0.02, adjusted for confounders). The corresponding values for pulse pressure increase was 15.5 \pm 14, 15.8 \pm 14, 17.4 \pm 14, and 17.8 \pm 15 mm Hg, respectively ($P=0.02$). Incidence of hypertension (\geq 160/95 mm Hg or treatment) and future blood pressure treatment showed similar associations with ISPs. Increase in diastolic blood pressure showed no association with ISPs.

Conclusions—Plasma levels of ISPs are associated with a future increase in blood pressure. This could contribute to the relationship between ISP levels and cardiovascular disease. (*Arterioscler Thromb Vasc Biol.* 2002;22:2054-2058.)

Key Words: inflammation ■ hypertension ■ epidemiology

Cross-sectional data have shown positive associations between blood pressure and different markers of inflammation.¹⁻⁵ The causal significance of this association is unclear. Some researchers have suggested that hypertension may promote inflammation.² Others have reported that the leukocyte count, a widely accepted marker of inflammation, is associated with the development of hypertension.⁶ However, whether inflammation-sensitive plasma proteins (ISPs) are risk factors for the development of hypertension is largely unknown.

We have previously reported that elevated levels of ISPs (ie, orosomucoid, α 1-antitrypsin, fibrinogen, haptoglobin, and ceruloplasmin) are associated with an increased incidence of cardiovascular diseases and that cardiovascular risk substantially increases if several of these proteins are elevated.⁷ The reason for this relationship is poorly understood. The present study explored the hypothesis that future blood pressure increase is associated with ISP levels.

Methods

Study Cohort

Between 1974 and 1983, 22 444 men participated in a screening program for the detection of individuals at high risk for cardiovas-

cular diseases.⁸ The participation rate was 71%. Plasma proteins were determined in 30% of the cohort, which was randomly selected. Complete information on 5 ISPs was available in 6193 men (mean age 46.8 \pm 3.7 years, range 28 to 61 years). Men with a history of myocardial infarction, stroke, cancer, and men undergoing treatment for hypertension (according to questionnaire) were excluded.

Between 1991 and 1996, approximately 40% of all 45- to 73 year-old men in the city of Malmö were examined as a part of the Malmö Diet and Cancer study.⁹ A total of 2262 men were re-examined. Figure summarizes the exclusions and drop-outs from the original cohort. Age at baseline ranged between 35 and 50 years. Mean follow-up was 15.7 \pm 2.2 years (range 9.5 to 21.5).

All men with medical treatment for hypertension at baseline were excluded. Men with treatment for hypertension at follow-up were included in the analysis of incidence of hypertension and blood pressure treatment. However, they were excluded from analyses of blood pressure increase (Figure).

Of the 5791 healthy men who were not receiving medication for hypertension at baseline, 422 died before the re-examination. Men who died were older (48.0 versus 46.7 years), had higher systolic blood pressure (SBP) (130.6 versus 128.1 mm Hg) and diastolic blood pressure (DBP) (87.4 versus 86.5 mm Hg), and had more often 2 or more ISPs in the top quartile (49 versus 32%) than men who survived. Compared with invited men who did not participate in the follow-up examination (n=2122), the present study cohort (n=2262) was fairly representative with respect to age and blood pressure (age,

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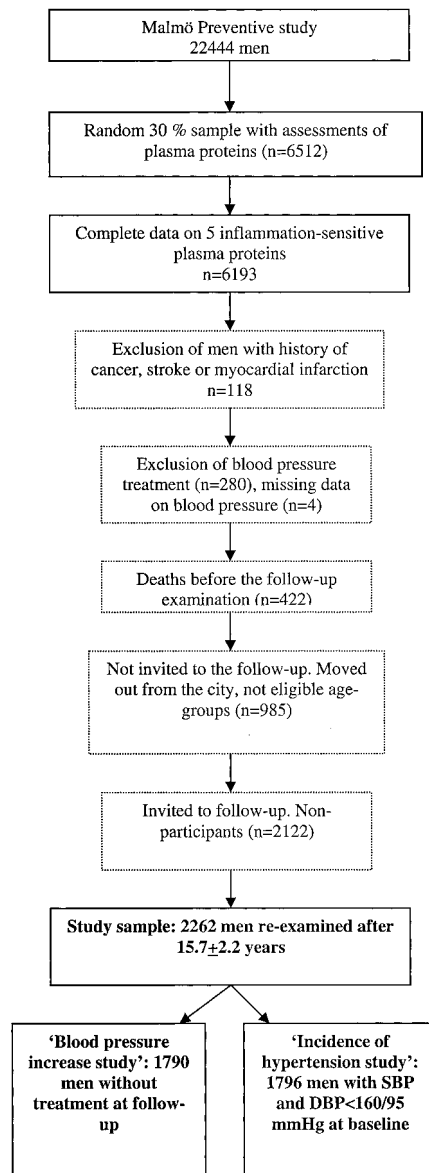
From the Departments of Community Medicine (G.E., L.J., B.H.), Internal Medicine (G.B., P.L., L.S.), and Vascular Diseases (F.L.), Malmö University Hospital, Malmö, Sweden.

Correspondence to Gunnar Engström, Department of Community Medicine, Malmö University Hospital, S-20502 Malmö, Sweden. E-mail Gunnar.Engstrom@smi.mas.lu.se

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Flow chart illustrating the study cohort.

46.6 versus 46.4 years; SBP, 127.5 versus 128.4 mm Hg; DSP, 86.1 versus 87.0 mm Hg). However, there were more men with 2 or more ISPs in the top quartile among nonparticipants (36.0 versus 28.2%).

Examination

Subjects were categorized into daily smokers and nonsmokers at baseline and at follow-up. Those who were smokers at the baseline examination and nonsmokers at follow-up were considered to have quit smoking during follow-up.

Blood samples were taken at the baseline examination after an overnight fast and analyzed at the laboratory of the university hospital. Plasma cholesterol and blood glucose was analyzed with standard methods. Men with a fasting whole blood glucose ≥ 6.7 mmol/L and men who reported receiving treatment for diabetes were considered as having diabetes.

Height and weight were measured at both examinations. Body mass index at baseline was calculated as $\text{weight}/\text{height}^2$ (kg/m^2). Weight increase was calculated as weight at baseline subtracted from the follow-up value. The waist and hip circumferences were measured by a trained nurse at the follow-up.¹⁰

Alcohol consumption was assessed at the follow-up examination. A menu book was used to record intake of alcoholic beverages during 7 consecutive days.¹⁰ Alcohol consumption (g/week) was log transformed because of the skewed distribution.

Education level and cohabitation status were assessed in a questionnaire at the follow-up examination. Education was divided into men who received a high school diploma or less ($n=1628$) and men who received a college degree or more ($n=630$). The sample was divided into men living alone ($n=354$) and men who lived with another person ($n=1878$). Information on education or cohabiting status was missing for 4 and 30 men, respectively.

ISPs

An electroimmunoassay method was used to assess the plasma levels of 5 proteins at baseline.¹¹ These proteins were used in clinical practice at the hospital to estimate inflammatory activity. The analyses were performed consecutively at the time of study entry. The correlation coefficients between the individual proteins range between 0.31 and 0.56.¹ We have previously shown that the cardiovascular risk increases with the number of elevated ISPs.⁷ The sample was therefore, in accordance with the previous study, categorized according to the number of proteins in the top quartile (fibrinogen >4.0 g/L, orosomucoid ($\alpha 1$ -glucoprotein) >0.93 g/L, $\alpha 1$ -antitrypsin >1.42 g/L, haptoglobin >1.76 g/L, and ceruloplasmin >0.36 g/L). Cronbach's α was calculated for this composite score ($\alpha=0.64$). The α -value indicates that this measure had an adequate reliability in terms of internal consistency and that the individual ISPs correlated well with the remaining sum score.

Blood Pressure

Blood pressure (mm Hg) was measured to the nearest 5 mm Hg after a 10-minute rest, with the subject in a lying position. A sphygmomanometer and a rubber cuff of appropriate size was used. At the follow-up examination, blood pressure was measured once after a 5-minute rest. The same equipment was used at both examinations. Blood pressure medication was assessed in a questionnaire at baseline. At the follow-up examination, blood pressure medication was assessed in a questionnaire and by asking the participants to bring all medicines to the examination. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Blood pressure increase (Δ SBP, Δ DBP, Δ PP) was calculated as the baseline value subtracted from the follow-up value. Hypertension was defined as SBP or DBP $\geq 160/95$ mm Hg or medical treatment for hypertension.¹² Prevalence of hypertension at follow-up was 47% with this definition.

Statistics

Correlations between blood pressure levels were assessed with Spearman rank correlations. Pearson's χ^2 and Mann-Whitney U test were used to compare incidence of hypertension and blood pressure increase for men with and without elevated protein levels. Logistic regression was used to assess treatment for hypertension and incidence of hypertension in relation to number of ISPs in the top quartile. Number of elevated ISPs was fitted as an ordinal variable. One-way ANOVA was used to assess the linear trends of blood pressure and blood pressure increase by number of elevated ISPs. This model was extended to an ANCOVA to adjust the relationships for potential confounders.

Results

Study Cohort

The baseline characteristics of the study cohort are presented in Tables 1 and 2. There were no significant relationships between blood pressure and ISP levels at baseline.

During the follow-up period, the percentage regular smokers decreased from 40% to 20%. Average weight increase was 4.3 ± 6.2 kg. Mean Δ SBP and Δ DBP were 19.4 ± 17.4 mm Hg and 3.3 ± 9.7 mm Hg, respectively, among

TABLE 1. Baseline Characteristics of the Study Cohort (n=2262)

Mean age, y	46.6±2.6
BMI, kg/m ²	26.3±3.4
Systolic BP, mm Hg	127±15
Diastolic BP, mm Hg	86±9.5
Normal blood pressure (<160/95 mm Hg), n (%)	1796 (79)
Treatment for hypertension, %	0
Smokers, %	40
Cholesterol, mmol/L	5.6±1.0
Diabetes, %	1.9
Physical inactivity, %	54
Plasma proteins, g/L	
Fibrinogen	3.43±0.77
α1-antitrypsin	1.25±0.26
Haptoglobin	1.27±0.63
Orosomucoid	0.80±0.20
Ceruloplasmin	0.31±0.07

those who were without antihypertensive medication at follow-up (n=1790). The corresponding values for those with antihypertensive medication at follow-up (n=472) were 15.8±21.3 and -0.9±12.3 mm Hg, respectively. Mean age and follow-up time were similar in the various ISP categories (Table 2).

Blood Pressure Increase in Men Without Treatment for Hypertension

A total of 1790 men reported, both at baseline and follow-up, that they were not treated for hypertension. The correlation between SBP at baseline and follow-up was $r_{sp}=0.43$ in this group. The corresponding values for DBP and PP were $r_{sp}=0.41$ and $r_{sp}=0.24$, respectively.

ΔSBP and ΔPP were significantly and positively associated with number of ISPs in the top quartile. This association remained significant after adjustments for several risk factors (Table 3). ΔDBP was not significantly associated with ISP levels.

The relationships with ΔSBP and ΔPP were similar for all individual ISPs (Table 4). No significant association was observed for ΔDSP.

The hypothesis that inferior socioeconomic circumstances explain the relationship between ISP and blood pressure increase was tested. Low education level and living alone (assessed at follow-up) was associated with higher ISP levels. However, education and cohabiting status showed no significant association with ΔSBP or ΔPP in the univariate analysis (data not shown). The relationships between ISP and future blood pressure increase (ie, ΔSBP, ΔPP) remained statistically significant when education and cohabiting status was included among the covariates.

Incidence and Treatment of Hypertension

A total of 1796 men had normal blood pressure at baseline (<160/95 mm Hg). In this group, 700 had hypertension at the follow-up examination, and 251 of them were receiving treatment for hypertension. Among men with initially normal blood pressure, hypertension and antihypertensive treatment at follow-up were positively and significantly associated with the number of elevated ISPs (Table 5). The association with future blood pressure treatment remained significant after adjustment for several confounders. The multivariate-adjusted association with incidence of hypertension almost reached significance ($P=0.07$). Further adjustments for education and cohabiting status did not change the results.

When the individual ISPs were analyzed separately, all ISPs showed similar relationships with incidence of hypertension, but the associations were weaker and sometimes nonsignificant (Table 4).

Discussion

The present results show that high plasma levels of ISP are associated with future blood pressure increase. The associations were weak and often nonsignificant for the individual ISP. However, the proteins added information to each other, similarly to what we previously reported for the incidence of cardiovascular disease.⁷ Incidence of hypertension was 46% among those with 3 elevated proteins, compared with 37% among those with no elevated proteins. Among men without treatment for hypertension, ΔSBP was approximately 3 mm Hg higher in those with 3 elevated proteins. To our knowledge, this is the first time these proteins have been associated with future blood pressure increase.

It is difficult to estimate the extent to which this relationship accounts for the increased incidence of stroke and myocardial infarction in men with high ISP levels. There are

TABLE 2. Baseline Blood Pressure in Relation to Inflammation-Sensitive Proteins in 2262 Men Without Treatment for Hypertension

	Inflammation-Sensitive Proteins in Top Quartile				P for Trend
	0 n=1046	1 n=579	2 n=303	3 or More n=334	
Blood pressure at baseline, mm Hg					
Systolic	126.7±13.5	128.3±15.2	128.8±16.9	127.1±15.2	0.20
Diastolic	85.5±9.0	86.9±9.7	87.1±10.2	85.9±9.6	0.09
Pulse pressure, mm Hg	41.2±9.4	41.5±10.2	41.7±11.2	41.2±10.3	0.79
Age at baseline, y	46.5±2.9	46.6±2.5	46.5±2.6	46.6±2.1	0.69
Follow-up time, y	15.8±2.2	15.8±2.2	15.6±2.4	15.6±2.2	0.20

TABLE 3. Blood pressure increase during follow-up in relation to inflammation-sensitive proteins at baseline (n=1790)

	Inflammation-Sensitive Proteins in Top Quartile				P for Trend	P for Trend*
	0 n=860	1 n=448	2 n=225	3 or More n=257		
ΔSBP, mm Hg	18.8±17.3	19.2±17.0	19.3±17.1	22.1±17.9	0.02	0.02
ΔDBP, mm Hg	3.2±9.8	3.4±9.4	1.9±10.1	4.3±9.4	0.60	0.25
ΔPP, mm Hg	15.5±14.3	15.8±14.1	17.4±13.9	17.8±14.9	0.01	0.02

*P for trend adjusted for age (at baseline), follow-up time, diabetes (at baseline), blood pressure (SBP, DBP, or PP [pulse pressure]) at baseline, cholesterol (at baseline), physical inactivity (at baseline), BMI (at baseline), smoking (at baseline), weight increase and smoking cessation during the follow-up period, alcohol consumption (at the follow-up examination), and waist-hip ratio (at follow-up).

reasons to assume that the results underestimate the true relationships between ISPs and blood pressure increase. First, the study was limited to survivors who participated in both examinations. Men who died before the follow-up examination (approximately 7%) had higher blood pressures and higher ISP levels, and it is likely that mortality was increased among the men whose blood pressure increased most. Second, men who received treatment for hypertension at baseline were excluded from all analyses, and those who received treatment at follow-up were excluded from the analysis of blood pressure increase. It could be assumed that blood pressure in most cases had increased before antihypertensive treatment was initiated. The exclusion of treated hypertensives, nonparticipants, and men who died during the follow-up also explains why no significant relationship between ISPs and blood pressure was observed at baseline. Because of the study design, we cannot claim that the sample is truly representative for the sample population, and the conclusions are thus based on the internal validity of the cohort.

The reason for the increased incidence of cardiovascular disease among subjects with high ISP levels is incompletely understood.¹³⁻¹⁵ These proteins may be associated with the development of atherosclerosis or destabilized atherosclerotic plaque; elevated ISP levels may be a result of preexisting atherosclerosis, or their actions may be mediated through other risk factors. Several explanations have been proposed, and more than one may be true.¹⁴ The present results show that ISP levels are associated with future increase in SBP and PP. PP is a marker of arterial stiffness,¹⁶ and it is possible that

the associations between ISP and future blood pressure increase may be explained by the development of atherosclerosis in individuals with high ISP levels.^{15,17,18} However, there could be other explanations for the relationship between ISP and future rise in PP, for example, inflammatory processes could be associated with an increased age-related deterioration of elastic fibers. Further studies are needed to establish whether the association between ISPs and future blood pressure increase is caused by an accelerated development of atherosclerosis or increased arterial stiffness from other causes. We have no information about the ISP levels at the follow-up examination. Whether men with hypertension develop more inflammation is thus another question for future studies.

Misclassification of exposure is a potential cause of bias in epidemiological studies. At the baseline examination, blood pressure was assessed twice at the same occasion. Subjects with treatment for hypertension at baseline were excluded. Blood pressure was measured once at follow-up. Blood pressure is characterized by large variation,¹⁹ and several repeated measurements should ideally be performed to reduce misclassification. However, the association between ISPs and blood pressure increase was statistically significant despite the possibility of a poor precision in the measurements of blood pressure.

Overweightness and obesity, physical inactivity, psychosocial factors, and family history have been identified as risk factors for hypertension.²⁰⁻²² However, the results were unaffected by adjustments for the most important risk factors for hypertension. No adjustments were made for family

TABLE 4. Increase in SBP and PP and Incidence of Hypertension in Relation to Individual ISP

	ΔSBP,‡ mm Hg	ΔPP,‡ mm Hg	Incidence of Hypertension,† %
α1-antitrypsin (Q1-3 vs Q4)	19.0±17 vs 20.7±18	15.8±14 vs 17.4±15*	38 vs 42
Ceruloplasmin (Q1-3 vs Q4)	19.2±17 vs 20.1±18	16.1±14 vs 16.5±14	39 vs 41
Fibrinogen (Q1-3 vs Q4)	18.9±17 vs 21.0±17*	15.8±14 vs 17.4±15*	37 vs 44*
Haptoglobin (Q1-3 vs Q4)	19.1±17 vs 20.7±18*	15.9±14 vs 17.0±14	38 vs 42
Orosomucoid (Q1-3 vs Q4)	19.0±17 vs 20.8±19*	15.8±14 vs 17.6±15*	38 vs 44*

Values are mean±SD or %.

Q indicates quartile.

*P<0.05 with Mann-Whitney U test or Pearson's χ².

†Percentage with hypertension (>=160/95 or treatment) at follow-up among 1796 men with normal blood pressure at baseline.

‡Based on 1790 men without blood pressure medication at both examinations.

TABLE 5. Hypertension and Treatment of Hypertension at Follow-Up in 1796 Men With Initially Normal Blood Pressure (<160/95 mm Hg) in Relation to Inflammation-Sensitive Proteins

	Inflammation-Sensitive Proteins in Top Quartile				P for Trend	P for Trend*
	0 n=851	1 n=438	2 n=235	3 or More n=272		
Treatment at follow-up, n (%)	100 (12)	57 (13)	45 (19)	49 (18)	0.001	0.03
Hypertension† at follow-up, n (%)	317 (37)	164 (37)	94 (40)	125 (46)	0.015	0.07

*P for trend adjusted for age (at baseline), follow-up time, diabetes (at baseline), SBP (at baseline), physical inactivity (at baseline), BMI (at baseline), cholesterol (at baseline), smoking (at baseline), weight increase and smoking cessation during the follow-up period, alcohol consumption (at the follow-up examination), and waist-hip ratio (at the follow-up examination).

† \geq 160/95 mm Hg or treatment for hypertension.

history. However, all results were adjusted for baseline blood pressure, which should account for most hereditary factors.²³ Smoking cessation is another potential confounder. Smoking is strongly associated with elevated ISP levels.¹ Although smoking is associated with lower blood pressure in most epidemiological studies, smoking cessation is associated with blood pressure increase.²⁴ However, smoking was assessed twice in the present study, and both smoking at baseline and smoking cessation during follow-up were taken into account in the analysis.

It is concluded that elevated ISP levels are associated with a future increase in SBP and PP among healthy middle-aged men. This association could contribute to the increased incidence of cardiovascular diseases among men with high ISP levels.

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