Inflammation, Abdominal Obesity, and Smoking as Predictors of Hypertension

Leo Niskanen, David E. Laaksonen, Kristiina Nyyssönen, Kari Punnonen, Veli-Pekka Valkonen, Ricardo Fuentes, Tomi-Pekka Tuomainen, Riitta Salonen, Jukka T. Salonen

Abstract—Development of hypertension has been linked to chronic low-grade inflammation. However, it is not known whether this connection is mediated by features of the metabolic syndrome or smoking, or their changes, which themselves have been linked to inflammation. We studied the predictive value of highly sensitive C-reactive protein (hs-CRP), smoking, and abdominal obesity to the development of hypertension in an 11-year follow-up of a population-based study cohort comprising 379 middle-aged normotensive men. During the follow-up, 124 men (33%) developed hypertension. Men with hs-CRP >3.0 mg/L were 2.8 (95% confidence interval, 1.2 to 6.6) more likely to develop hypertension than with hs-CRP <1.0 mg/L even after adjustment for features of the metabolic syndrome, lifestyle factors, and their changes. Cigarette smoking was also associated with development of hypertension independently of inflammation and other confounders. Waist girth increased more in men who quit smoking than in other men. An increase in waist girth during follow-up strongly predicted incident hypertension. The decrease in smoking was not associated with a lower risk of hypertension in age-adjusted analyses. Hypertension is preceded by low-grade chronic inflammation in middle-aged white men independently of smoking or features of the metabolic syndrome. Furthermore, smoking may be a risk factor for hypertension. Although stopping smoking is beneficial with respect to health outcomes, the subsequent increase in weight and waist girth associated with smoking cessation may offset the decrease in the risk of hypertension that one may otherwise expect. (Hypertension. 2004;44:859-865.)

Key Words: obesity ■ smoking ■ prospective studies ■ insulin resistance

Chronic low-grade inflammation seems to be an early feature of many chronic degenerative disorders, including atherosclerosis, abdominal obesity, and type 2 diabetes.1-3 These disorders are also commonly associated with hypertension, which itself has also been linked recently to inflammation. The most compelling evidence comes from the Women’s Health Study, in which C-reactive protein (CRP) as a marker of low-grade inflammation predicted the development of hypertension in a cohort of 20 525 female US health professionals during a follow-up of 7.8 years.4 This effect was seen even in those with low baseline blood pressure levels and in those without other conventional cardiovascular risk factors, but no adjustment could be made for the presence of the metabolic syndrome, a possible mediator of this connection.5

Smoking causes an acute rise in blood pressure, whereas the connection between chronic smoking and development of hypertension is still unclear. Smoking in its own right increases inflammation,6 but smoking cessation may not reverse it.7 Furthermore, stopping smoking commonly leads to weight gain. Weight gain is a well-established risk factor for hypertension. Moreover, weight gain and obesity, especially abdominal, appear to not only cause inflammation but may be preceded by inflammation.8 Complicating the picture, increased alcohol intake is associated with hypertension and smoking but possibly decreased abdominal fat.9

Observational studies are hampered with problems when describing these intertwined phenomena. If we are to understand chronic low-grade inflammatory processes in relation to the multifactorial origin of hypertension, the ideal study setting should describe various pathways leading to hypertension by taking into account the changes in these factors. In this study, we assessed the predictive value of low-grade inflammation in the development of hypertension in middle-aged men during an 11-year follow-up, controlling for baseline blood pressure, various lifestyle factors, features of the metabolic syndrome, and also the changes in smoking, alcohol intake, and waist girth during follow-up. Furthermore, we evaluate the role of smoking independently of inflammation and changes in waist girth with the development of hypertension.
Methods

Participants
Subjects were participants of the Kuopio Ischemic Heart Disease Risk Factor Study.10 Participants were a random age-stratified sample of men living in Eastern Finland who were 42, 48, 54, or 60 years old at the baseline examination from 1987 to 1989. The recruitment and study design have been described previously in detail.10 Repeat examinations for those who had undergone carotid ultrasound at baseline were performed from 1991 to 1994 (4-year follow-up) and 1998 to 2001 (11-year follow-up). In all, 854 men participated in the 11-year follow-up (90% of those alive). Men with hypertension or diabetes at baseline were excluded, leaving 379 men for analyses of incident hypertension during the 11-year follow-up. The university ethics committee approved the study. All participants gave their written informed consent.

Definition of Hypertension
Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley and Sons). The protocol included 3 measurements while supine, 1 while standing, and 2 while sitting, with 5-minute intervals between measurements. The mean of the 2 sitting measurements was used as the systolic and diastolic blood pressure. Hypertension was defined at baseline and follow-up as systolic blood pressure \( \geq 140 \text{ mm Hg} \), diastolic blood pressure \( \geq 90 \text{ mm Hg} \), or use of antihypertensive medication.11,12

Anthropometric and Biochemical Measurements
Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m\(^2\)). Waist circumference was defined as the average of 2 measurements taken at the midpoint between the lowest rib and the iliac crest after inspiration and expiration.

Fasting blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Diabetes was defined as fasting blood glucose concentration \( \geq 6.1 \text{ mmol/L} \) (equivalent to plasma glucose \( \geq 7.0 \text{ mmol/L} \)) or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment.13 Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk). HDL fractions were separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically. Fibrinogen was measured based on the clotting of diluted plasma with excess thrombin.

Measurement of Highly Sensitive CRP
Serum CRP was measured with an immunometric assay (Immulite High Sensitivity CR Assay; DPC).14 We used CRP cut-offs of 1.0 mg/L and 3.0 mg/L, as recommended by the Center for Disease Control and the American Heart Association.15 To limit confounding with acute infection or occult disease, we excluded men with CRP concentrations \( \geq 10.0 \text{ mg/L} \).

Other Assessments
Assessments of medical history and medications, smoking, alcohol consumption, adult socioeconomic status, and moderate-to-vigorous leisure-time physical activity have been described previously.16,17 Dietary intake of saturated fat, sodium, potassium, and fruits and vegetables was measured with 4-day food records as grams per day and adjusted by regression analysis for energy intake.18 High-resolution B-mode ultrasonography was used to examine a 1.0- to 1.5-cm section at the distal end of the left and right common carotid artery proximal to the carotid bulb, as explained in detail previously.19

Statistical Analyses
Differences in baseline characteristics between men who developed hypertension and those who did not were assessed with Student t test, and where indicated, the \( \chi^2 \) test. Fibrinogen is an acute phase reactant and as such, a marker of inflammation that has a high correlation with CRP levels \( (r=0.50) \). To avoid problems with multicollinearity, we adjusted fibrinogen by CRP using linear regression before including it in the logistical regression models. To investigate the associations of CRP concentrations with hypertension, CRP concentrations were categorized using the cut-offs \( <1.0 \text{ mg/L} \), 1.0 to 2.9 mg/L, and 3.0 to 9.9 mg/L.14 Cigarette smoking was categorized as not at all, 1 to 19 cigarettes per day, and \( \geq 20 \) cigarettes per day. Alcohol intake was converted into grams of ethanol per week and classified as none at all, 1 to 83 g per week, and \( \geq 84 \) g per week (84 g of ethanol is \( \approx 7 \) drinks). Waist circumference was categorized into thirds (only 17% and 3% of nonhypertensive men had waist girths \( >94 \) and 102 cm, values that have been recommended as “action levels” for prevention of chronic disease).20 The variables in question were entered into logistic regression models adjusting for age and potential mediators or confounding variables. The association of changes in waist circumference, smoking (as cigarettes per day), and alcohol intake with incident hypertension were similarly analyzed as continuous variables in logistic regression models. The covariates for the logistic regression models were forced into the model. Variables are given as means \( \pm \) SD, except for variables with a skewed distribution (CRP, insulin, triglycerides, alcohol intake, and physical activity), which are given as medians and interquartile ranges, and proportions, which are given as percentages. In analyses using continuous variables, skewed variables were log transformed. The mean was substituted for missing values (n=10 to 23) of covariates. Statistical significance was considered to be \( P<0.05 \). All statistical analyses were performed with SPSS 11.0 for Windows.

Results

Baseline Clinical Characteristics
During the 11-year follow-up, men who developed hypertension were heavier, had a larger waist, and were more dyslipidemic at baseline (Table 1). They also had higher blood pressure. The prevalence of the metabolic syndrome was uncommon in these relatively lean men without hypertension or diabetes but was more common in those who developed hypertension during the follow-up. Smokers more commonly developed hypertension, but the change in the number of cigarettes smoked did not differ between men who developed and did not develop hypertension. Alcohol intake was similar in both groups, but increased alcohol intake at the 4-year follow-up was more common in men who developed hypertension by the 11-year follow-up. Baseline CRP concentrations were much higher in men who later developed hypertension.

CRP at Baseline and Hypertension
Men with CRP concentrations \( \geq 3 \text{ mg/L} \) were 3.6\( \times \) more likely to develop hypertension than men with levels \( <1.0 \text{ mg/L} \) in age-adjusted analyses (Table 2). Adjustment for baseline blood pressure, lifestyle factors, and cardiovascular disease (model 2) only marginally weakened the association. After additional adjustment for features of the metabolic syndrome at baseline (model 3) or further for changes in waist circumference, number of cigarettes smoked per day, or intake of alcohol (model 4) during the first 11 years of follow-up, men with CRP levels \( \geq 3 \text{ mg/L} \) were still 2.8\( \times \) more likely to develop hypertension during the 11-year follow-up. Adjustment for changes in waist girth, smoking, or alcohol intake over the 4-year period gave similar results as model 4. Adjustment for development of cardiovascular disease during follow-up also had little effect on the results. Inclusion of BMI in models 2 through 4 in place of or in
addition to waist girth had little effect on the results. CRP-adjusted fibrinogen was not associated with incident hypertension, and inclusion of CRP-adjusted fibrinogen in the models did not affect the association of CRP with incident hypertension. The risk associated with CRP levels was graded, and men with levels between 1.0 and 3.0 mg/L were also at increased risk for developing hypertension. CRP concentrations also predicted incident hypertension at 11 years even after adjustment for the average maximum thickness of the intima carotid for the left and right carotid arteries in addition to technical covarates (odds ratio [OR] for CRP, 3 mg/L versus 1 mg/L 2.4 to 2.9 in models 2 to 4; P=0.001 to 0.017 for the trend). CRP levels ≥3.0 mg/L were quite uncommon (n=39) in these relatively lean men without hypertension or diabetes at baseline, but the results were very similar when using tertiles to categorize CRP (data not shown). CRP concentrations also predicted use of blood pressure medication at 11 years (OR for CRP, ≥3 mg/L versus <1 mg/L 3.1 to 3.5 in all models; P=0.005 to 0.016 for the trend) and incident hypertension when defining hypertension at the 11-year follow-up solely by systolic and diastolic blood pressure rather than including medication in the definition (data not shown). There was no evidence of modification of the association of CRP with hypertension after stratification by median systolic blood pressure, BMI, or smoking status.

Smoking at Baseline and Hypertension
Men who smoked ≥20 cigarettes per day were more than twice as likely to develop hypertension (Table 2). Additional adjustment for features of the metabolic syndrome at baseline (model 3) weakened the association. However, after taking

### TABLE 1. Baseline Characteristics of Men Who Developed Hypertension During Follow-Up and Those Who Did Not

<table>
<thead>
<tr>
<th>Descriptive Variables</th>
<th>Nonhypertensive at Follow-Up</th>
<th>Hypertensive at Follow-Up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>255</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.2 (6.6)</td>
<td>51.8 (6.7)</td>
<td>0.021</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>28</td>
<td>44</td>
<td>0.002</td>
</tr>
<tr>
<td>Change in smoking during follow-up (for smokers)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 years (n=133), cigarettes per day</td>
<td>−3 (11)</td>
<td>−4 (9)</td>
<td>0.88</td>
</tr>
<tr>
<td>At 11 years (n=132), cigarettes per day</td>
<td>−8 (15)</td>
<td>−4 (13)</td>
<td>0.14</td>
</tr>
<tr>
<td>Alcohol consumption, g/week</td>
<td>31 (6, 87)</td>
<td>28 (7, 89)</td>
<td>0.83</td>
</tr>
<tr>
<td>Change in alcohol intake during follow-up (for nonabstainers)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 years (n=314), g/week</td>
<td>−5 (119)</td>
<td>22 (74)</td>
<td>0.026</td>
</tr>
<tr>
<td>At 11 years (n=346), g/week</td>
<td>4 (150)</td>
<td>25 (112)</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>24</td>
<td>28</td>
<td>0.32</td>
</tr>
<tr>
<td>Maximum carotid intima thickness, mm</td>
<td>0.88 (0.78, 0.98)</td>
<td>0.91 (0.80, 1.05)</td>
<td>0.005</td>
</tr>
<tr>
<td>Adult socioeconomic status score</td>
<td>6.9 (3.9)</td>
<td>6.8 (4.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 (9)</td>
<td>128 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79 (6)</td>
<td>84 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.1 (2.7)</td>
<td>26.1 (2.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>85.3 (7.9)</td>
<td>88.3 (8.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in waist girth during follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 years</td>
<td>4.4 (4.1)</td>
<td>5.3 (3.9)</td>
<td>0.052</td>
</tr>
<tr>
<td>At 11 years</td>
<td>7.1 (5.8)</td>
<td>8.7 (5.9)</td>
<td>0.015</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.6 (0.9)</td>
<td>4.0 (1.1)</td>
<td>0.067</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L/L</td>
<td>1.40 (0.29)</td>
<td>1.28 (0.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L/L</td>
<td>0.96 (0.75, 1.38)</td>
<td>1.0 (0.83, 1.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol /L/L</td>
<td>4.48 (0.45)</td>
<td>4.52 (0.47)</td>
<td>0.42</td>
</tr>
<tr>
<td>Fasting serum insulin, pmol/L/L</td>
<td>7.9 (6.2, 10.3)</td>
<td>8.9 (7.0, 11.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>Fibrinogen (g/L, unadjusted)</td>
<td>2.81 (0.50)</td>
<td>3.02 (0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome (NCEP), %</td>
<td>1.0</td>
<td>3</td>
<td>0.026</td>
</tr>
<tr>
<td>Moderate and vigorous LTPA, min/week</td>
<td>143 (62, 256)</td>
<td>128 (56, 241)</td>
<td>0.24</td>
</tr>
<tr>
<td>Serum CRP, g/dL</td>
<td>0.81 (0.50, 1.46)</td>
<td>1.24 (0.76, 2.33)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means (SD), medians (interquartile ranges), or percentages. Higher adult socioeconomic status score means lower socioeconomic status.

NCEP indicates National Cholesterol Education Program29,30; LTPA, leisure-time physical activity.
into account the changes in waist circumference, number of cigarettes smoked per day, or in the intake of alcohol (model 4) during the 11-year follow-up, smoking at baseline was associated with a graded increase in the risk of hypertension during the 11-year follow-up. The increase in risk of smoking in model 4 compared with model 3 was a result of adjustment for the change in smoking, alcohol intake, and waist circumference. Adjustment for the changes in waist girth, smoking, or alcohol intake during the 4-year period gave essentially identical results as adjustment for changes during the 11-year follow-up.

### Alcohol Intake at Baseline and Hypertension

Men reporting consumption of ≥7 drinks per week were 1.5× more likely than nondrinkers to develop hypertension during the 11-year follow-up in age-adjusted analyses, but the association was not significant (Table 2). The ORs attenuated even further in multivariate analyses.

### Incident Hypertension and Changes in Smoking, Alcohol Intake, and Waist Girth

Of the changes in smoking, alcohol intake, and leisure-time physical activity, only the changes in smoking and alcohol intake were associated with incident hypertension. When adjusting for only age and baseline smoking, the change in the number of cigarettes smoked was not associated with development of hypertension (Table 3). However, with further multivariate adjustment, the association strengthened, which was attributable mainly to the inclusion of baseline waist girth and HDL cholesterol levels in model 3 and to the inclusion of the change in waist girth to model 4. The association of the change in number of cigarettes smoked per day was not associated with incident hypertension in age-adjusted analyses, but the association was stronger in multivariate analyses, particularly when adjusting for changes in waist girth and lifestyle factors during the 11-year follow-up.
day during the 11-year follow-up with incident hypertension was significant also in analyses confined to smokers (eg, in models 2 to 4; OR, 0.42 to 0.56 for a 10-cigarette decrease; \( P = 0.021 \) to 0.006). The relevance of taking into account the change in waist girth in the association of the change in smoking with development of hypertension is also illustrated by the increase in waist circumference with smoking cessation. The waist girth of nonsmokers who remained nonsmokers increased 7.3 cm (95% confidence interval [CI], 6.6 to 8.1), and that of smokers at baseline who remained smokers increased 7.0 cm (95% CI, 5.7 to 8.3) during the 11-year follow-up. In contrast, the waist girth of men who quit during the follow-up increased by 10.4 cm (95% CI, 8.7 to 12.2; \( P = 0.003 \)) for the difference between groups after adjustment for age and baseline waist girth). An increase in alcohol intake also increased the risk of hypertension during the 11-year follow-up. Of the changes during follow-up in the metabolic variables shown in model 3, only the change in waist girth was associated with development of hypertension (Table 3). Multivariate adjustment had little effect on the association.

### Discussion

This study extends the findings of Women’s Health Study\(^4\) of chronic low-grade inflammation as a predictor of hypertension in men. Moreover, this association is not explained by various lifestyle factors or features of the metabolic syndrome.

Although hypertension is another member of a long list of disorders preceded by low-grade inflammation, the mechanisms of the mediating factors remain elusive. Based on the results of this study, inflammation as measured by highly sensitive CRP concentrations is clearly more than a marker of abdominal obesity or the metabolic syndrome and is not explained by smoking or presence of cardiovascular disease. There could well be an underlying genetic propensity, although little data currently exist to support this conviction.

On the other hand, low-grade inflammation as measured by CRP levels could still be a marker of highly active cytokine-producing adipose tissue infiltrated by macrophages and leading to complement activation and release of vasoactive cytokines and subsequent endothelial dysfunction;\(^8,21\) and any increase in the amount of fat tissue, especially in the abdominal area, could lead to more active function and development of hypertension. This mechanism is unlikely to explain a major part of the association of CRP levels with incident hypertension because adjustment for waist girth and other variables related to the metabolic syndrome only slightly attenuated the association. Elevated CRP concentrations may also be secondary to artery wall thickening and atherosclerotic burden, but adjustment for carotid intima thickness did not alter the predictive value of CRP. CRP itself may cause endothelial dysfunction;\(^22\) Furthermore, CRP may upregulate angiotensin type 1 receptors, leading to proliferation of vascular smooth muscle cells;\(^23\) and subsequently to hypertension.

In this study, the predictive role of smoking with development of hypertension was somewhat surprising. Middle-aged men who decreased the number of cigarettes smoked daily by 10 were not less likely to develop hypertension in age-adjusted analyses. However, when taking into account waist at baseline and the increase in waist girth in addition to other variables, decreasing the number of cigarettes smoked by 10 halved their adjusted risk of hypertension. Thus, even smok-
cing cessation did not seem to protect from hypertension, most likely because of the associated increase in abdominal obesity. There are previous reports suggesting that smoking or smoking cessation may indeed be a harbinger for development of hypertension, but generally, smoking has not been considered a causative factor of hypertension. One of the mechanisms may be smoking-induced renal damage.28

Alcohol intake was weakly associated with development of hypertension, and after multivariate adjustment, the connection was abolished. On the other hand, an increase in alcohol intake during the follow-up was clearly associated with a higher incidence of hypertension. The overall weak association of alcohol intake with incident hypertension may be attributable to the difficulty in the reliable recording of alcohol intake.

The strengths of this study are the population-based prospective design, high participation rate, detailed assessment of variables related to lifestyle, and the metabolic syndrome and use of a uniform and constant definition of hypertension with careful measurement of blood pressure according to a standard protocol. Importantly, the changes of major variables related to lifestyle and the metabolic syndrome during follow-up were determined. The limitations are that of the various inflammatory markers, only a single baseline measurement of CRP was taken into account. However, this, if anything, leads to conservative estimate of the association in question. The study was performed in middle-aged white men, and generalization to other groups should be viewed with caution.

Perspectives

We have demonstrated that hypertension is preceded by low-grade chronic inflammation as assessed by CRP in middle-aged white men. This connection was not explained by smoking, baseline systolic blood pressure, or features of metabolic syndrome. Furthermore, smoking may be a risk factor for hypertension. Although stopping smoking is extremely beneficial with respect to cardiovascular risk and other health outcomes, the subsequent weight gain and increase in waist girth associated with smoking cessation may offset the decrease in risk of hypertension that one may otherwise expect. Therefore, efforts to curtail smoking should also take more seriously into account the consequences of the subsequent weight gain because the early prevention of abdominal obesity may be easier than later attempts at weight loss and control of hypertension. This study illustrates that multiple pathways seem to lead to hypertension independently of inflammation, including an increase in waist girth and smoking, even when the relevant changes during the follow-up are taken into account.

Acknowledgments

The Kuopio Ischemic Heart Disease Risk Factor Study was supported by grants from the Academy of Finland (grants 41471, 45155, 1041086, and 2041022), the Ministry of Education of Finland (grants 167/72296, 157/722/97, and 156/722/98), and the National Heart, Lung, and Blood Institute of the United States (grant HL44199). We thank the staff of the Research Institute of Public Health, University of Kuopio, and Kuopio Research Institute of Exercise Medicine for data collection in the Kuopio Ischemic Heart Disease Risk Factor Study.

References


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Hypertension. 2004;44:859-865; originally published online October 18, 2004; doi: 10.1161/01.HYP.0000146691.51307.84
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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