Original Article

Metabolic Disorders Predict Development of Hypertension in Normotensive Japanese Subjects

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Each component of the metabolic syndrome is not necessarily clustered coincidentally. Thus, subjects who have obesity, dyslipidemia or impaired glucose tolerance may be at high risk for the development of hypertension. We studied the predictive value of the following for the development of hypertension: obesity (body mass index ≥ 25.0 kg/m²), dyslipidemia (high-density lipoprotein-cholesterol < 40 mg/dL, triglyceride ≥ 150 mg/dL, or use of anti-dyslipidemic drugs), high normal blood pressure (130 mmHg $\leq$ systolic < 140 mmHg, or 85 mmHg $\leq$ diastolic < 90 mmHg), and impaired glucose tolerance (fasting plasma glucose ≥ 110 mg/dL or use of anti-diabetic agents). This observational study included 5,785 subjects without hypertension recruited from participants in our health checkup program. They were followed up for 1,097 $\pm$ 365 d, with the endpoint being the development of hypertension. During the follow-up, hypertension developed in 1,168 subjects (74.1 per 1,000 person-years). The incidence of hypertension was higher in subjects who had obesity (106.2 vs. 67.8), dyslipidemia (96.1 vs. 69.0), high normal blood pressure (166.0 vs. 40.1), or impaired glucose tolerance (130.5 vs. 65.3 per 1,000 person-years) than in those without these disorders at baseline. The risk of hypertension was increased as the number of metabolic disorders in an individual increased. Multiple regression analysis indicated that obesity, high normal blood pressure, and impaired glucose tolerance remained independent predictors of the onset of hypertension. Thus, the presence of individual components of the metabolic syndrome predicts the development of hypertension. Prediction of the development of hypertension may lead to effective prevention of both hypertension and resulting cardiovascular diseases. (*Hypertens Res* 2008; 31: 665–671)

Key Words: body mass index, high-density lipoprotein cholesterol, impaired glucose tolerance, metabolic syndrome, triglycerides

Introduction

Hypertension is one of the major risk factors of cardiovascular diseases, including myocardial infarction, stroke, and peripheral artery disease (1). Because the lifetime risk of developing hypertension is very high, reducing its incidence,

if possible, may effectively prevent cardiovascular disease (2–4). The prevention of hypertension is thus an attractive public health goal.

In recent years there has been a worldwide increase in the incidence of the metabolic syndrome (6–9), which is identified by the presence of three or more of the following risk factors: obesity, elevated triglycerides, decreased high-density

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Fig. 1. Flow of subjects through the study.

lipoprotein cholesterol, elevated blood pressure, and elevated fasting plasma glucose (5). This syndrome is thought to be associated with an increased risk of all-cause and cardiovascular disease mortality as well as with an increased incidence of cardiovascular disease (7, 9–13). The metabolic syndrome's root causes are obesity and genetic factors, and it is closely associated with hypoadiponectinemia and insulin resistance (14–19). A number of clinical studies have demonstrated the importance of fat distribution, especially the contribution of visceral fat accumulation, in the development of metabolic syndrome (16, 18–20). Thus, the components of the syndrome are not clustered coincidentally, but form a series of related factors tending to co-occur in the same individual (16, 17). This concept leads to the speculation that subjects with “metabolic disorders” such as obesity, dyslipidemia, or glucose intolerance are at high risk for the development of hypertension. Thus, the present study was designed to investigate the predictive values of individual components of the metabolic disorders in the development of hypertension.

Methods

Study Design

This was an observational study to assess the impact of individual components of the metabolic disorders on the development of hypertension in normotensive subjects. We undertook the study in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Enshu Hospital. All patients gave informed written consent to participate prior to the start of the study. The subjects were followed up by investigators at Enshu Hospital.

Study Subjects and Procedures

Participants who visited our hospital for a yearly health checkup between July 2000 and March 2002 ($n=9,639$) were screened for eligibility for inclusion in the present study. Par-

Table 1. Baseline Characteristics of Subjects

	Total ($n=5,785$)
Age (years)	52.5 ± 11.8
Gender: male (n (%))	3,634 (62.8%)
Follow-up period (d)	$1,097 \pm 365$
Body mass index (kg/m^2)	22.4 ± 2.8
Systolic blood pressure (mmHg)	119.0 ± 12.4
Diastolic blood pressure (mmHg)	73.1 ± 8.6
Yearly increase in mean blood pressure (mmHg/year)	1.1 ± 5.3
Heart rate (bpm)	63.5 ± 9.7
Fasting plasma glucose (mg/dL)	98.9 ± 18.9
Total cholesterol (mg/dL)	206.8 ± 34.4
Low-density lipoprotein cholesterol (mg/dL)	122.6 ± 31.1
High-density lipoprotein cholesterol (mg/dL)	61.8 ± 15.6
Triglyceride (mg/dL)	109.5 ± 73.3
CCr (mL/min)	95.6 ± 24.1
Uric acid (mg/dL)	5.2 ± 1.4
Hemoglobin (g/dL)	14.5 ± 1.5
Current smoking (n (%))	1,767 (30.5%)

Data were expressed as the mean $\pm$ SD except for gender, follow-up period and current smoking. Follow-up period was expressed as median $\pm$ median absolute deviation. CCr was estimated using the Cockcroft-Gault formula. CCr, creatinine clearance.

ticipants under medical treatment for hypertension were excluded. Among the rest of the subjects, the checkup program (including a routine physical examination, chest X-ray, electrocardiogram, and laboratory assessment of cardiovascular risk factors) revealed that 6,094 subjects had no hypertension, and they were enrolled in the present study. We planned to follow up the subjects for 5 years, with the endpoint being the development of hypertension. During follow-up, blood pressure was measured every year. Since 309 subjects could not be followed up, the data on 5,785 subjects who completed the follow-up were finally analyzed (Fig. 1). The relationship between body mass index (BMI), lipid profile, the presence of high normal blood pressure or glucose intolerance at enrollment, and the incidence of hypertension during the follow-up period were evaluated.

Definition of Hypertension and Metabolic Disorders

Blood pressure was measured after the subjects sat for 5 min in a chair with their backs supported. Systolic and diastolic blood pressure levels were recorded as the first and fifth Korotkoff phases, respectively, using a mercury sphygmomanometer with their arms supported at heart level. Three consecutive blood pressure measurements separated by intervals of 2 min were taken, and the mean of the second and third

Fig. 2. New onset of hypertension during follow-up.

Table 2. Metabolic Disorders and Risk of Hypertension

	Hypertension development (per 1,000 person-years)	Relative risk (95% CI)
Metabolic disorders		
Obesity (–) (<i>n</i> =4,787)	67.8	1 (reference)
Obesity (+) (<i>n</i> =998)	106.2	1.48 (1.43–1.52)
Dyslipidemia (–) (<i>n</i> =4,636)	69.0	1 (reference)
Dyslipidemia (+) (<i>n</i> =1,149)	96.1	1.35 (1.31–1.39)
High normal blood pressure (–) (<i>n</i> =4,045)	40.1	1 (reference)
High normal blood pressure (+) (<i>n</i> =1,740)	166.0	3.57 (3.48–3.66)
Impaired glucose tolerance (–) (<i>n</i> =4,964)	65.3	1 (reference)
Impaired glucose tolerance (+) (<i>n</i> =821)	130.5	1.87 (1.80–1.93)
Number of metabolic disorders		
0 (<i>n</i> =2,703)	33.1	1 (reference)
1 (<i>n</i> =1,855)	87.4	2.58 (2.52–2.64)
2 (<i>n</i> =886)	146.9	3.90 (3.77–4.03)
3 (<i>n</i> =283)	176.3	4.38 (4.13–4.64)
4 (<i>n</i> =58)	209.3	5.16 (4.53–5.87)

CI, confidence interval.

measurements was recorded as the blood pressure. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medications. The metabolic disorders were defined as follows: obesity, BMI ≥ 25.0 kg/m²; dyslipidemia, high-density lipoprotein-cholesterol < 40 mg/dL, triglyceride ≥ 150 mg/dL, or the use of anti-dyslipidemic medications; high normal blood pressure, 130 mmHg $\leq$ systolic blood pressure < 140 mmHg, or 85 mmHg $\leq$ diastolic blood pressure < 90 mmHg; impaired glucose tolerance, fasting plasma glucose ≥ 110 mg/dL or the use of anti-diabetic medications.

Statistical Analysis

All analyses were performed using StatView 5.0 (SAS Institute, Cary, USA). Data in the text and tables are expressed as the mean $\pm$ SD except for the duration of the follow-up period (median $\pm$ median absolute deviation). Differences between two means with normal distribution were compared by unpaired Student's *t*-test. Yates' corrected χ^2 test was used for comparisons between categorical data. The cumulative rate of the new onset of hypertension was examined using the Kaplan-Meier method. We used multivariable Cox propor-

Fig. 3. Results of multivariable Cox proportional hazards regression analyses demonstrating the hazards ratios (HRs) for the risk of developing hypertension according to baseline metabolic disorders (adjusted by age, gender, creatinine clearance, uric acid, and smoking habit at baseline). IGT, impaired glucose tolerance.

tional hazard regression models adjusting for known risk factors to examine the relationships between metabolic disorders and the development of hypertension. Odds ratios and 95% confidence intervals (CIs) were calculated. In addition, multiple linear-regression analysis was performed using BMI, the presence of dyslipidemia, mean blood pressure, the presence of impaired glucose tolerance, age, gender, creatinine clearance calculated by the Cockcroft-Gault formula, and uric acid at baseline as independent variables, and changes in mean blood pressure per year as a dependent variable. A change in mean blood pressure was calculated as an increase in mean blood pressure divided by the follow-up period (years). In subjects who started antihypertensive medication during follow-up, changes in mean blood pressure were calculated using data prior to the prescription of antihypertensive drugs. A *p* value <0.05 was considered significant.

Results

Baseline characteristics of subjects are presented in Table 1. Some subjects were under medication for dyslipidemia ($n=188$, 3.2%) or diabetes mellitus ($n=177$, 3.1%). The study was completed as planned; the actual follow-up was 15,760 person-years, and the median follow-up period was 1,097 d. During the follow-up period, hypertension developed in 1,168 subjects (20.2%; 74.1 per 1,000 person-years) (Fig. 2), with the incidence being more frequent in male subjects ($n=851$, 23.4%; 84.8 per 1,000 person-years) than in female subjects ($n=317$, 14.7%; 55.4 per 1,000 person-years, $p<0.0001$). The incidence of hypertension was closely related to the presence of metabolic disorders at baseline; subjects who had obesity, dyslipidemia, high normal blood pressure, or impaired glucose tolerance were more likely to develop hypertension than were those without such disorders (Fig. 2 and Table 2). Interestingly, an increase in the number

of metabolic disorders in each individual at baseline markedly increased the likelihood of hypertension developing during follow-up (Table 2). Cox proportional hazards regression analyses indicated that BMI, high normal blood pressure, and impaired glucose tolerance remained independent predictors of the development of hypertension after adjustment for age, gender, creatinine clearance, uric acid, and smoking habit (Fig. 3). Multiple linear-regression analysis was applied to investigate possible determinant variables for yearly increases in mean blood pressure (Table 3). An increase in mean blood pressure was positively correlated with BMI and the presence of impaired glucose tolerance at baseline, and inversely associated with mean blood pressure at baseline after adjustment for age, gender, creatinine clearance, and uric acid (Table 3).

Discussion

The present study demonstrated that obesity or the presence of dyslipidemia, elevated blood pressure (high normal blood pressure), or impaired glucose tolerance is closely associated with the development of hypertension in subjects without hypertension. Furthermore, obesity and glucose intolerance are each significant determinants of a yearly increase in mean blood pressure. Although the increase in mean blood pressure does not necessarily mean that hypertension will develop, this finding suggests the important role of metabolic disorders in the development of hypertension. The fact that the risk of the development of hypertension was dramatically increased when metabolic disorders overlapped further reinforces this concept. As the predictive value of metabolic disorders is highly significant, subjects at high risk for the development of hypertension are easily extracted from the general population using a simple screening procedure. Prediction of the new onset of hypertension is quite important, because the develop-

Table 3. Multiple Regression Analysis Demonstrating the Relation between Increases in Mean Blood Pressure/Year and Variables Obtained at Baseline (Adjusted by Age, Gender, Creatinine Clearance, and Uric Acid)

Variables at baseline	$r^2=0.109, F=86.75, p<0.0001$		
	Standardized coefficient	<i>t</i>	<i>p</i>
BMI	0.092	5.45	<0.0001
Dyslipidemia	0.011	0.80	0.43
MBP	-0.383	-25.0	<0.0001
IGT	0.037	2.82	0.005

BMI, body mass index; MBP, mean blood pressure; IGT, impaired glucose tolerance.

ment of hypertension may be prevented or postponed by lifestyle modification (21) or pharmacological treatment (22).

The mechanism underlying our findings that the presence of metabolic disorders predicts the development of hypertension is not clear. However, the present results strongly support the concept that obesity, dyslipidemia, elevation of blood pressure, and impaired glucose tolerance are closely related in their etiology. Each metabolic disorder may develop from the common base that is associated with genetic factors and lifestyle (16, 17). Among the factors related to lifestyle, the accumulation of visceral fat may be the root cause (16, 18, 19). These speculations are compatible with previous findings that elevated C-reactive protein predicts the development of hypertension (23, 24). Indeed, chronic inflammation is closely associated with obesity and the metabolic syndrome (25–28). In multiple Cox regressions where baseline values of covariates were included, each metabolic disorder except dyslipidemia was independently associated with the development of hypertension. Although we have defined obesity as BMI ≥ 25 kg/m², an increase in BMI is not identical to the accumulation of visceral fat. This may be why high normal blood pressure and impaired glucose tolerance each predicted the development of hypertension independent of BMI. The present study does not reject the concept that the accumulation of visceral fat basically contributes to the development of metabolic disorders.

The strongest predictor of hypertension in the present study was increased blood pressure within the normal level, confirming the findings of previous studies (29, 30); however, mean blood pressure at baseline was inversely correlated with the increase in mean blood pressure during follow-up. This seems inconsistent with the former finding, but a great increase in blood pressure does not always mean that hypertension will develop. High normal blood pressure is a precursor of hypertension (29, 30) and is associated with excess morbidity and death from cardiovascular causes (31). These associations of high blood pressure may be caused, at least in part, by the co-existence of other metabolic disorders in this population, as speculated from the present results. Among

various factors related to lifestyle, obesity, excess sodium, and insufficient potassium intake, reduced physical activity, insufficient intake of fruits and vegetables, and excess alcohol consumption have been identified as causal factors for hypertension (32–34). Moreover, abdominal obesity predicted hypertension in a cohort study comprising middle-aged normotensive men (35). The present results are compatible with some of the findings mentioned above, because the risk from the development of hypertension was increased by 47.7% and 35.1% in subjects who had obesity or dyslipidemia, respectively, as compared to those without such disorders. The Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruits, vegetables, and low-fat dairy products and low in saturated fat, total fat, and cholesterol, has been proved to reduce blood pressure (36, 37). The antihypertensive effect of the DASH diet may be attributable, at least in part, to an improvement in metabolic disorders, because body weight, fasting plasma glucose, and triglycerides are reduced and high-density lipoprotein cholesterol is increased with this diet protocol (36).

Interpretation of the data is limited due to the following conditions: 1) blood pressure was measured only once a year, 2) subjects were participants in a yearly physical checkup program, 3) subjects under medication (other than for hypertension) were included, and 4) BMI was used to assess overweight status. Furthermore, the results would be altered if a different definition of dyslipidemia or high normal blood pressure were used. These should be noted when interpreting the present data. Since the present study offers the significant concept that metabolic disorders may predict the development of hypertension, this should be confirmed by further studies with a large number of subjects. The effect of the improvement of metabolic disorders on the likelihood of the development of hypertension and cardiovascular disease should also be investigated.

The present findings clearly indicated that subjects at elevated risk for the development of hypertension can be extracted from the general population by a simple medical checkup that assesses metabolic disorders. Hypertension is the principal risk factor of cardiovascular diseases, and its prevalence worldwide is very high (1–4). Thus, the prevention of increases in blood pressure is one of the most effective strategies for reducing cardiovascular disease. Toward this end, the identification of subjects who are at increased risk of developing hypertension is quite an attractive approach. Indeed, metabolic disorders that are related to the development of hypertension are, fortunately, of a modifiable nature; however, there is thus far no evidence that improvement of metabolic disorders prevents the onset of hypertension. This should be elucidated by further studies. Pharmacological intervention using an angiotensin receptor blocker has proved to be effective to reduce the risk of hypertension in subjects with high normal blood pressure (22). This may be another approach to reduce the incidence of hypertension, especially in high-risk subjects with overlapping metabolic disorders.

These preventive approaches target subjects who have not previously been important targets in the primary prevention of cardiovascular diseases due to their mild or borderline, but not critical, metabolic disorders. However, the large size of this population suggests that this approach is an attractive public health goal.

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