Original Article

Impact of Multiple Risk Factor Clustering on the Elevation of Blood Pressure

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A family history of hypertension, obesity, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia have all been associated with risk of hypertension. We retrospectively conducted a longitudinal study in a large screened cohort to explore the effect of the clustering of these five risk factors on the elevation of blood pressure (BP) in normotensive subjects at baseline. The study group comprised 4,857 normotensive subjects not treated with antihypertensive drugs (systolic BP < 140 mmHg, diastolic BP < 90 mmHg, 3,111 men and 1,746 women) who were followed up from 1997 to 1999. By 1999, 360 subjects had BP at the hypertensive level (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). The incidence of subjects whose BP became hypertensive was 37 per 1,000 person-years. After adjusting for age, sex, systolic BP and other clinical factors, multiple logistic analysis showed that the relative risk of BP elevation was 1.49 (95% CI: 1.09 to 2.05) in subjects with one risk factor; 1.65 (95% CI: 1.15 to 2.27) in those with two risk factors; 1.42 (95% CI: 0.91 to 2.32) in those with three; and 4.86 (95% CI: 2.58 to 9.16) in those with four or more when compared with subjects with no risk factors. Multiple regression analysis showed that the number of risk factors was positively correlated with an increase in BP from 1997 to 1999; the regression coefficient was 0.51 (p < 0.001) for increase in systolic BP, and 0.31 (p = 0.008) for increase in diastolic BP after adjusting for age and sex. In conclusion, clustering of risk factors significantly predicted the development of hypertension. (Hypertens Res 2002; 25: 811–816)

Key Words: family history, obesity, diabetes mellitus, triglyceride, total cholesterol

Introduction

Hypertension is a potent cardiovascular risk factor (1, 2) that increases the risk of cardiovascular diseases, especially stroke and coronary heart disease (3). Elevation of blood pressure (BP) is also a strong independent risk factor for end-stage renal disease (4, 5). Despite improvements in detection and treatment, there is no evidence of a decline in the prevalence of hypertension over the past four decades. Family history of hypertension (6–9), obesity (10), hypercholesterolemia (11, 12), hypertriglyceridemia (11, 12), and diabetes mellitus (13) are all associated with increased risk of hypertension. Although these five factors are each significant risks for hypertension, it has not been confirmed whether the clustering of these factors raises the risk of developing hypertension.

In our previous cross-sectional study on a screened cohort, we reported that risk factor clustering is significantly associated with the prevalence of hypertension (14). The aim of the present study was to investigate whether the clustering of risk factors actually raises the risk of hypertension in subjects who are normotensive at baseline.
Methods

Study Design

The factors investigated in the screening in which the present subjects participated were described previously (9, 14). The screening, run by the Okinawa General Health Maintenance Association, involves a thorough physical examination of 10,000 adults each year. There were 6,403 subjects who participated in the program in both 1997 and 1999. Among these 6,403 subjects, 4,857 normotensive subjects (systolic BP < 140 mmHg and diastolic BP < 90 mmHg, and without antihypertensive medication) were enrolled in the study. A history of hypertension, the presence of diabetes mellitus, smoking habits, alcohol consumption, and physical exercise habits were determined by self-administered, standardized questionnaires. Questionnaire results were confirmed in an interview with a physician. A history of hypertension in probands and family members was established by asking subjects if, to their knowledge, their parents or siblings had high BP or were treated for hypertension. A positive family history of hypertension was defined as the reported presence of hypertension in parents or siblings. Information regarding offspring was not considered.

Blood was drawn in the morning after overnight fasting. After 15 min of sitting, BP was measured twice by a trained nurse using a standard sphygmomanometer. The lower of two BP measurements was used for this study. Height, body weight, BP, fasting blood sugar, glycosylated haemoglobin (HbA1c), total cholesterol, and triglyceride were measured in all subjects. Body mass index (BMI) was calculated as body weight (kg) divided by the square of the height (m²).

Definition of Outcome Measures and Risk Factors

The main outcome measure in logistic analysis was the elevation of BP in 1999 to a hypertensive level (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) (15). Baseline risk factors at 1997 were defined as follows: obesity, BMI ≥ 25 kg/m² (16); diabetes mellitus, fasting blood glucose level ≥ 126 mg/dl (7 mmol/l) (17), HbA1c > 7.0%, or subject treated with drug therapy; hypercholesterolemia, total cholesterol ≥ 220 mg/dl (5.69 mmol/l) (18); hypertriglyceridemia, triglyceride > 150 mg/dl (1.7 mmol/l) (19).

Statistical Analysis

The unpaired Student’s t-test or χ² test was used to compare values or ratios between groups. The relative risk for the elevation of BP to a hypertensive level in subjects with risk factors was estimated with the use of logistic regression models (StatView 5.0, SAS Institute, Cary, USA). Trends of incidence were tested by multiple regression analysis, and values of p < 0.05 were considered to indicate statistical significance.

Results

Baseline Clinical Data

Of the 4,857 subjects, 360 (250 men, 110 women) developed hypertension during the 2 years of the study. The incidence of BP elevation was 7.4% (8.3% in men; 6.4% in women). Baseline characteristics are presented in Table 1. Subjects whose BP rose to a hypertensive level by 1999 tended to be obese older men. Hypertensive subjects were also more like-
ly to have hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, a higher baseline systolic and diastolic BP, and a higher frequency of positive family history of hypertension than those who remained normotensive. As compared to normotensive subjects in 1999, the rate of current smokers was lower and the rate of habitual exercisers was higher in hypertensive subjects.

Relative Risk for the Elevation of BP to a Hypertensive Level in Patients with Risk Factors

Logistic regression analysis revealed that all five baseline clinical factors (family history of hypertension, obesity, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia) were statistically significant risk factors for the elevation of BP to a hypertensive level after adjusting for age, sex, cigarette-smoking status, alcohol-drinking status, and physical exercise in analysis A (Table 2). However, when baseline systolic BP was added to the variables adjusted in analysis B (Table 2), the significant association between hypertension and each of diabetes mellitus, hypercholesterolemia and hypertriglyceridemia was lost. In analysis B, baseline systolic BP (mmHg) was a significant predictor of hypertension: the relative risk was 1.12 (95% confidence interval (CI): 1.10 to 1.14, \( p < 0.0001 \)). The relative risk of smoking was also significant 0.83 (0.75 to 0.93), \( p = 0.0009 \), but that of physical exercise was not 1.03 (0.92 to 1.14), \( p = 0.55 \), after adjusting for age and sex.

Relation of Clustering Risks to the Elevation of BP to a Hypertensive Level

Table 3 shows the relation of the number of risk factors in subjects at baseline to the presence or absence of hypertension. After adjusting for age and sex, the incidence of BP elevation to a hypertensive level during the 2 years increased from 3.6% to 12.5% with the accumulation of risk factors. The relative risks of BP elevation were also significant in subjects with one to four or more risk factors compared to those in subjects with no risk factors. Even after adjusting for systolic BP at baseline, these relative risks were significant (Table 3, analysis B).

The mean levels of systolic and diastolic BP in 1997 and 1999 according to the number of risk factors are shown Fig. 1. Each mean of systolic and diastolic BP for subjects with one through four or more risks was higher than that for subjects with no risks in both years. Both systolic and diastolic BP increased significantly from 1997 to 1999 in the subjects with one through four or more risks, whereas no significant increase was observed in the subjects with no risk factors. Multiple regression analysis showed that the number of risk factors was positively correlated to BP after controlling for...
age and sex. The regression coefficient was 1.78 (t = 11.9, p < 0.0001) for systolic BP in 1997, 1.38 (t = 12.4, p < 0.0001) for diastolic BP in 1997, 2.29 (t = 13.3, p < 0.0001) for systolic BP in 1999, and 1.69 (t = 1.69, p < 0.0001) for diastolic BP in 1999.

Mean increases in systolic BP (ΔSBP) and diastolic BP (ΔDBP) from 1997 to 1999 are shown in Fig. 2. Age- and sex-adjusted multiple regression analysis showed that the number of risk factors was positively correlated to ΔSBP and ΔDBP. The regression coefficient was 0.51 (t = 3.2, p = 0.001) for ΔSBP and 0.31 (t = 2.61, p < 0.008) for ΔDBP.

Discussion

After adjusting systolic BP at baseline, family history of hypertension and obesity in normotensive subjects were independent risk factors for the elevation of BP to a hypertensive level. In addition, even after adjusting systolic BP at baseline, the clustering of five risk factors—i.e., a family history of hypertension, obesity, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia—increased the risk of BP elevation in normotensive subjects. These observations may have important clinical implications with regard to the prevention of hypertension and suggest that the clustering of risk factors plays an important role in the pathogenesis of hypertension.

The incidence of hypertension has been established in several population studies. The Framingham Heart Study (20) showed that hypertension occurred in 228 men (22%) and 207 women (16%) over 8 years in subjects who were normotensive at baseline. This rate corresponds to 5.5% in men and 4.0% in women over 2 years. A cohort study of normotensive Hispanic and non-Hispanic white southern Colorado residents revealed that the hypertension incidence rate was 28 per 1,000 person-years (21). In the Paris Prospective Study (22), the incidence of hypertension was 78.9 per 1,000 person-years in 4,149 Caucasian, non-hypertensive, non-diabetic middle-aged men. The 2-year cumulative incidence of the elevation of BP to a hypertensive level in the present study (7.4%, or 37 per 1,000 person-years) was higher than the incidence of hypertension reported in the two American studies and lower than that in the Paris Prospective Study. Differences of age and sex ratios of the subjects in addition to general variation may be related to the difference in incidence.

Family history of hypertension was a significant predictor of BP elevation in the present study. A family history of hypertension increased the risk of hypertension by 80% (Table 2). In addition, we previously reported that the number of first-degree family members with hypertension was correlated with the risk of hypertension (9). Therefore, those who have a family history of hypertension should be informed of their risk of hypertension and educated about the benefits of weight control (23), avoiding high salt-intake (24), and limiting their alcohol intake (25).

Obesity is another known risk factor for hypertension (26, 27). The association of BMI and BP has been extensively reported (28). Furthermore, the odds ratio of hypertension has been shown to be reduced by 77% with long-term weight reduction (29). However, the prevalence of obesity has increased significantly in Japan (30–32). There is thus an ur-
gent need in primary healthcare for more effective measures of weight reduction. Although it has been suggested that obese patients exhibiting sympathetic nervous system overactivity during weight loss are resistant to weight loss-induced BP reduction (33), mild aerobic exercise and a mild hypocaloric diet should be effective for reducing not only BP but also multiple cardiovascular risk factors (34). A regular exercise program should also be beneficial for BP control (35).

Metabolic diseases such as dyslipidemia (36) and diabetes (37) are common in hypertensive patients. Total cholesterol and triglyceride levels were significantly associated with BP levels in the Tromsø study (11). Hyperinsulinemia is much more prevalent in Japanese-American subjects with a positive family history of hypertension (38) and other independent predictors for developing hypertension (39). In a study by Eriksson et al., the complications of impaired glucose tolerance or diabetes mellitus, hyperinsulinemia, and hypertriglyceridemia were found in 6% of all hypertensives, or twice as frequently as in the normotensive population (12). Itoh et al. reported that weight reduction during a 3-month therapeutic dietary and exercise program was significantly and positively associated with BP reduction and improvement of hyperinsulinemia (40). The present study also suggests that the complication of metabolic disturbances increases the risk for BP elevation.

Hypertension is usually associated with multiple risk factors (14). Risk of cardiovascular disease and all-cause mortality increases substantially with each additional risk factor from current smoking, obesity, hypertension, high blood cholesterol, and diabetes (41). Our data suggest that normotensives with multiple risk factors have a high risk for elevation of BP. Therefore, even in normotensives, appropriate risk stratification and risk profile modification are needed to prevent hypertension.

In the Framingham study, it was reported that subjects with normal or high normal blood pressure had an increased risk of hypertension compared to those with optimal blood pressure at baseline (42). In the present study, elevated baseline systolic BP was associated with a risk of developing hypertension. Furthermore, as a risk of hypertension, elevated baseline systolic BP seemed to be superior to diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia, because the significance of those variables in predicting hypertension was lost after adjusting for systolic BP (Table 2).

Cigarette smoking induces an acute rise in BP and plasma catecholamines (43). Systolic ambulatory BP increased during the daytime period in smokers (44). However, a large number of epidemiologic studies (45) have reported that smokers have lower BP than nonsmokers. In the present study, smoking showed a significant negative odds ratio for development of hypertension. In many epidemiologic studies, the BP might be examined during abstinence in smokers, and discrepancies in the results of these studies may be due to this. The results of previous studies indicate that the BP of smokers tends to be high during smoking but low during abstinence. And although several mechanisms have been proposed to explain the low blood pressure in smokers, it remains to be determined which, if any, of these mechanisms are operative (45).

In summary, the clustering of risk factors has a significant impact on the risk of elevation of BP. In addition, the number of risk factors is positively related with the increase in levels of both systolic and diastolic BP. These data suggest that clustering of risk factors plays an important role in the pathogenesis of hypertension.

Acknowledgements

We thank Mr. M. Itoh and Mr. K. Shiroma of the Okinawa General Health Maintenance Association for their provision of data.

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