Original Article

Proteinuria as a Significant Determinant of Hypertension in a Normotensive Screened Cohort in Okinawa, Japan

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To evaluate the influence of proteinuria on the development of hypertension in normotensive screened subjects. We studied 4,428 normotensive subjects without heart disease (2,888 men, 1,540 women, age 19–89 years) who were participants in a 1-day health evaluation in both 1997 and 2000. The 3-year frequency of developing hypertension was 6.0% in subjects without proteinuria, and 13.5% in subjects with proteinuria. The odds ratio for developing hypertension by age (year) increased approximately 1.6%. Obesity was associated with an approximately 40% increased risk of hypertension; proteinuria increased the risk of hypertension 2-fold. Proteinuria was a significant predictor of developing hypertension. Age, obesity, and initial blood pressure level also contributed to the development of hypertension. In conclusion, proteinuria is a powerful predictor of developing hypertension. Age and obesity are also associated with increased risk of hypertension. Lifestyle modification might thus be necessary, particularly in subjects with proteinuria. (*Hypertens Res* 2006; 29: 687–693)

***Key Words*: hypertension, frequency, risk factor, proteinuria, obesity**

Introduction

Many epidemiologic studies report that hypertension is the most important cardiovascular risk factor and is closely related to mortality rate (*1–6*). Thus, primary prevention of hypertension is an essential public issue. Various epidemiologic studies have also reported that chronic kidney disease and proteinuria are powerful predictors of cardiovascular events and death (*7*). JNC VII (*8*) and ESC/ECS guidelines for the management of arterial hypertension (*9*) indicate that chronic kidney disease or microalbuminuria are major risk factors.

Chronic kidney disease and proteinuria are usually considered markers of target organ damage, and proteinuria is also considered a marker of systemic vascular damage (*10*, *11*). In the clinical setting, there are sometimes subjects with proteinuria that do not have hypertension. If proteinuria is representative of the early phase of systemic vascular damage, even in normotensive subjects, it might predict future hypertension. To our knowledge, however, there have been no studies of the association between proteinuria and the development of hypertension. Accordingly, the aim of the present study was to evaluate the association between proteinuria and developing hypertension in normotensive subjects in Okinawa, Japan.

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Table 1. Baseline Characteristics of the Study Subjects According to Proteinuria

Variables	Proteinuria		*p*
	No (*n*=4,213)	Yes (*n*=147)	
Age (years)	46.8±9.2	48.2±9.1	0.0540
Systolic blood pressure (mmHg)	115±11	119±10	<0.0001
Diastolic blood pressure (mmHg)	71±8	74±8	0.0002
Body mass index (kg/m^2)	23.8±2.9	25.2±3.0	<0.0001
Total cholesterol (mg/dl)	205±35	215±39	0.0005
HDL-C (mg/dl)	56±14	53±14	0.0132
Triglyceride (mg/dl)	140±113	177±133	<0.0001
GFR (ml/min/1.73 m^2)	75±23	81±25	0.0021
Diabetes mellitus	170 (4)	27 (18)	<0.0001
Current smoking	1,339 (32)	47 (32)	0.9612
Current drinking	2,846 (68)	108 (73)	0.1314
Habitual exercise	1,481 (35)	63 (43)	0.0771

Values are mean±SD or number of the subjects (%). HDL-C, high-density lipoprotein-cholesterol; GFR, glomerular filtration rate.

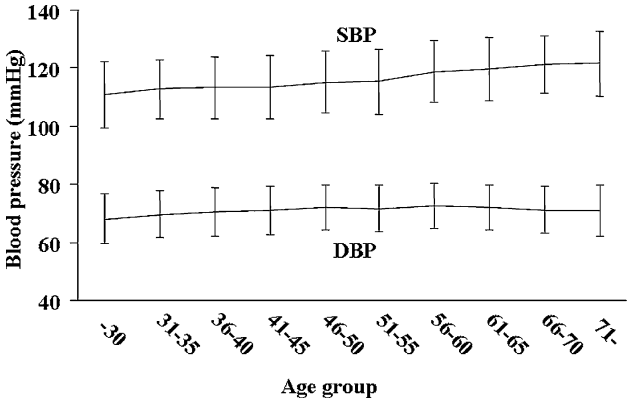

Fig. 1. *Relation between age and blood pressure change. Screening was performed from April 1997 to March 1998. Values are mean±SD.*

Methods

Study Subjects

The subjects of the present study were participants of a 1-day health evaluation held by the Okinawa General Health Maintenance Association (OGHMA), which is one of the largest screening centers in Okinawa, Japan (*12*). OGHMA offers a 1-day health evaluation program throughout the year. This program provides thorough anthropometric measurements, physical examination, laboratory tests, and electrocardiography, both for individuals and for health maintenance programs of companies and public organizations.

Study participants were eligible for inclusion in the present investigation if they participated in this health evaluation program in both 1997 and 2000, and if they were free of the following exclusion criteria: hypertension (systolic blood pressure [SBP]≥140 mmHg, or diastolic blood pressure [DBP]≥90 mmHg, or the use of antihypertensive medication at the 1997 screening), a lack of urinalysis data, a history of heart disease, or the use of medication for heart disease. Subjects with overt proteinuria (+++ or over) or hematuria (++ or over) were also excluded because they were suspected of having renal disease.

The present study was conducted in accordance with the principles of the Declaration of Helsinki 1975, as revised in 1993. Data for this study were provided after approval from the ethics committee of the OGHMA. All data concerning identifying information of the screenees were excluded from the original registry.

Data Collection

Individual histories of hypertension, diabetes mellitus, hyperlipidemia, and smoking, drinking, and exercise habits were determined by self-administered questionnaires and confirmed by a physician's interview. Data for the lifestyle-related factors were based on the self-administered questionnaires administered in 1997. Blood sampling was performed after overnight fasting. Trained nurses measured SBP and DBP twice using a standard sphygmomanometer with an appropriate-sized cuff after the subject sat quietly for 15 min. In the present study, the lower blood pressure (BP) value was used to classify participants into three non-hypertensive JNC VI/World Health Organization–International Society of Hypertension (WHO-ISH) BP categories: optimum (SBP<120 mmHg and DBP<80 mmHg), normal (SBP 120–129 mmHg or DBP 80–84 mmHg), or high normal BP (SBP 130–139 mmHg or DBP 85–89 mmHg) at the examination in 1997. We reclassified subjects according to their BP status at the examination in 2000. Body mass index (BMI) was calculated as body weight (kg) divided by the square of the height

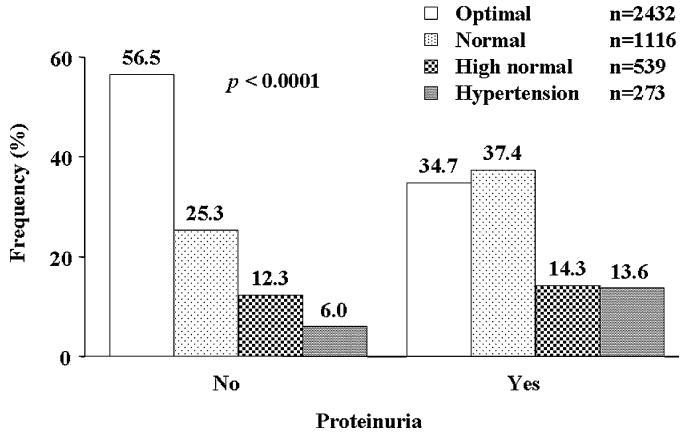

Fig. 2. *Frequencies of subsequent blood pressure levels by the presence or absence of proteinuria.*

(m^2). Obesity was defined as BMI ≥ 25.0 kg/m^2. Diabetes mellitus was defined as fasting blood glucose concentration ≥ 126 mg/dl (7 mmol/l), HbA1c ≥ 6.5%, or the taking of medication for these conditions. Hypercholesterolemia was defined as total cholesterol ≥ 220 mg/dl (5.69 mmol/l), and hypertriglyceridemia was defined as serum triglyceride ≥ 150 mg/dl (1.7 mmol/l). Proteinuria was defined positive as (±) or over by dipstick. The glomerular filtration rate was calculated using the method of Cockcroft and Gault (*13*), and the body surface area was calculated using the method of DuBois and DuBois (*14*).

Calculation of Annual Frequency of Hypertension

We derived the annual frequency of hypertension for proteinuria group from the corresponding 3-year rate, assuming it was constant risk (*15*). Thus, if R is the 3-year rate of progression to hypertension, then $Q=(1-R)^{1/3}$ indicates the annual probability of not progressing to hypertension. The annual probability of progression to hypertension, P_1, equals $1-Q$. Similarly, the 2-year (P_2) probability of developing hypertension is: $P_2=1-Q^2$.

Statistical Methods

We used multivariate logistic regression analysis to examine the association between proteinuria and the risk of developing hypertension. Odds ratios (OR) and 95% confidence intervals (95% CIs) were computed in increments for continuous variables or as a change in category for categorical variables. We used three logistic regression models to assess the OR and 95% CI for developing hypertension: a model adjusted for age, sex, current smoking habit, current drinking habit, habitual exercise, and initial SBP (Model 1); a model adjusted for age, sex, glomerular filtration rate, current smoking habit, current drinking habit, habitual exercise, and initial BP category (Model 2); and a model adjusted for age, sex, glomerular filtration rate, current smoking habit, current drinking habit, habitual exercise, and initial SBP (Model 3). All analyses were performed with StatView 5.0 software (SAS Institute, Cary, USA). We used one-factor ANOVA or χ^2 test to analyze the association between proteinuria and variables. Two-tailed probability values of less than 0.05 were considered statistically significant.

Results

Of 5,923 eligible screenees, 1,563 were excluded because of hypertension ($n=1{,}408$; men 1,010, women 398), a lack of urinalysis data ($n=3$; men 0, women 3), overt proteinuria or hematuria ($n=68$; men 9, women 59), history of heart disease, or the use of medication for heart disease ($n=99$; men 74, women 25) in 1997. Therefore, 4,360 subjects (2,879 men, 1,481 women, from 19 to 89 years of age) were enrolled for the present analysis.

At the baseline (1997) examination, 4,213 (97%) subjects did not have proteinuria and 147 (3%) had proteinuria. Dipstick scores for subjects with proteinuria were 111 (±), 35 (+), and 1 (++). Of 4,213 subjects, 2,305 (56%) had optimum BP, 1,147 (28%) had normal BP, and 635 (16%) had high normal BP. Clinical characteristics of all subjects grouped by proteinuria are summarized in Table 1. Subjects with proteinuria had significantly higher SBP, DBP, BMI, total cholesterol, triglycerides, glomerular filtration rate, and frequency of diabetes mellitus, and slightly but not significantly lower high density lipoprotein cholesterol level. Smoking frequency, drinking habits, and exercise habits were not statistically different between the two groups.

There was a specific age-related BP pattern in this cohort. The SBP showed a consistent linear increase with age, and this rise became steeper after the fifth decade (Fig. 1). The DBP patterns indicated an early rise and late plateau or fall with a transition from age 50 to 60 years.

The relation between proteinuria and the frequencies of

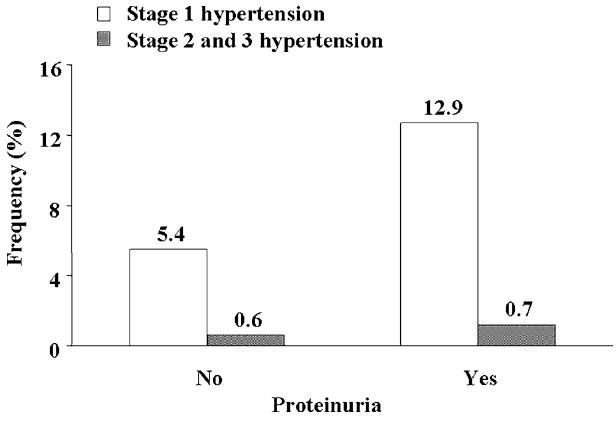

Fig. 3. *The 3-year frequency of the development of hypertension for each initial blood pressure category.*

each BP category at the follow-up period are shown in Fig. 2. Within the 3-year period, 273 subjects (6.3%) progressed to hypertension. The subsequent BP level in the subjects with proteinuria was significantly higher than that in the subjects without proteinuria ($p<0.0001$). The frequency of developing hypertension varied according to the presence or absence of proteinuria. Subjects with proteinuria more often developed severe hypertension (Fig. 3). The estimates of 1-year, 2-year, and 3-year crude frequencies of developing hypertension are summarized in Table 2. The annual frequency of developing hypertension in subjects with proteinuria was 2.4-fold higher than that in subjects without proteinuria. Initial BP levels were also a significant predictor of developing hypertension. Compared with optimum BP, a normal BP at baseline was associated with a 4.8-fold increased risk of hypertension, while high normal BP was associated with a 13.6-fold raised OR (Table 2). This is consistent with a previous report (*15*).

Table 3 shows the OR and 95% CI of developing hypertension for each factor. These results indicate that proteinuria was associated with an approximately 2-fold increased risk of developing hypertension regardless of renal function and initial BP status (Table 3). In addition to proteinuria, age and obesity were significant predictors of hypertension. Obesity was associated with a 40% to 70% increased risk for developing hypertension.

Discussion

Proteinuria is a well-known marker of target organ damage and is the most potent predictor of end-stage renal disease (*12*). A population-based study demonstrated that subjects with proteinuria have higher overall and cardiovascular mortality rates than those without proteinuria (*11*). A Japanese population-based study demonstrated that microalbuminuria was an effective marker for the presence of a high number of cardiovascular risk factors and advanced arterial stiffness (*16*). Moreover, several studies have demonstrated that

Table 2. Frequency of Developing Hypertension

Variables	1 year*	2 years*	3 years
Proteinuria			
No (%)	2.0	4.0	6.0
Yes (%)	4.8	9.3	13.6
Initial BP category			
Optimal BP (%)	0.5	1.1	1.6
Normal BP (%)	2.4	4.7	7.0
High normal BP (%)	6.8	13.1	19.0

BP, blood pressure. *Estimated frequencies of hypertension.

microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in nondiabetic populations (*17–19*). Proteinuria has recently been a focus of attention because of its association with both kidney disease and cardiovascular disease. JNC VII (*8*) and ESC/ECS guidelines for the management of arterial hypertension (*9*) regard microalbuminuria as a major cardiovascular risk factor.

In hypertensive subjects, elevated intraglomerular filtration pressure leads to albumin leakage from the glomeruli, and this phenomenon is considered to be one of the mechanisms of microalbuminuria. There is a relationship between blood pressure and microalbuminuria, even in normotensive subjects (*20*). Thus, BP is closely related with proteinuria regardless of the BP status. Our cohort also demonstrated that BP was significantly higher in subjects with proteinuria than in subjects without proteinuria (Table 1). In this situation, proteinuria would not be a marker of target organ damage. However, our results indicate that proteinuria is a predictor of future hypertension regardless of the initial BP level. Moreover, proteinuria has a higher OR for future hypertension than age and obesity. This means that the presence of proteinuria could be a powerful predictor of future hypertension. Table 1 shows that subjects with proteinuria had a higher glomerular filtration rate than those without proteinuria. At the same time, we should emphasize that proteinuria is a predictor of the development of hypertension independent of renal function. These findings indicate that proteinuria might not be the result of hypertension or target organ damage, but rather a significant predictor of developing hypertension. The present study supports our preliminary report (*21*). In this regard, the present study supports our preliminary report (*21*). Thus proteinuria might not be a benign condition, but a rather serious condition, even if subjects are normotensive.

The annual frequency of the development of hypertension in our cohort was lower than that in previous studies (*15*, *22*). There were several reasons for this. First, our subjects were at lower risk (younger age, lower BMI) than those of one of the other studies (*15*). Second, because we had no data for medication use in 2000, the BP status of our subjects could only be judged by their BP readings, which may have led to an underestimation of the frequency of the development of hypertension. There have been several Japanese studies examining the

Table 3. Factors Associated with Developing Hypertension

Variables	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.037**	1.022–1.052	1.013	0.995–1.032	1.011	0.992–1.029
Diabetes mellitus	1.219	0.731–2.031	1.081	0.693–1.828	1.072	0.631–1.820
Hypercholesterolemia	1.179	0.899–1.545	1.080	0.815–1.391	1.080	0.815–1.432
Hypertriglyceridemia	0.836	0.626–1.117	0.738	0.548–0.994	0.744	0.552–1.003
Obesity	1.662**	1.281–2.155	1.356	0.993–1.852	1.273	0.932–1.739
Proteinuria	2.091**	1.262–3.463	1.898*	1.123–3.208	1.815*	1.069–3.208

*$p<0.05$, **$p<0.005$. Model 1: model adjusted for sex, current smoking habit, current drinking habit, habitual exercise, and initial SBP. Model 2: model adjusted for sex, glomerular filtration rate, current smoking habit, current drinking habit, habitual exercise, and initial BP category. Model 3: model adjusted for sex, glomerular filtration rate, current smoking habit, current drinking habit, current exercise, and initial SBP. OR, odds ratio; 95% CI, 95% confidence interval; SBP, systolic blood pressure.

incidence of hypertension and the factors associated with its development (*23–27*). However, the subjects of some of these studies have not been representative of the general population (*25*, *26*), and in other studies the sample size was too small (*23–25*). In fact, there has been only one large cohort study on the development of hypertension in the general Japanese population (*27*). According to that community-based study (*27*), the estimated annual frequency of the development of hypertension is 2.6% in men and 2.8% in women, which values are similar to those in the present study. This means that the frequency of the development of hypertension in the Japanese might be lower than that of Western countries.

The age-related increase in BP indicated a linear rise in SBP, but an early rise and a late fall in DBP, a divergent rather than parallel tracking pattern (*28*, *29*). In this cohort, all the subjects were normotensive, and had the same age-related BP pattern (Fig. 1). Aging is frequently associated with increased BP and development of hypertension. Age was not a significant factor of the future risk of hypertension in the multivariate analysis (Table 3, Model 1 and Model 2), most likely due to the formula that we used for calculating the glomerular filtration rate (*13*). Because this formula includes the age of subjects, age is not likely to have been a significant factor for the development of hypertension in the multivariate model. In fact, age was a significant factor for developing hypertension in Model 1 (Table 3).

Obesity, baseline BMI, and weight gain during the follow-up were the important determinants of the development of hypertension, as previously reported (*15*, *30*, *31*). Moreover, it has previously been reported that weight reduction can lower BP (*32*, *33*). These findings suggest that obesity and weight gain predict the future risk of hypertension, and that weight control is important for the primary prevention of hypertension (*34*). Our results also showed that obesity was a significant predictor of the development of hypertension (Table 3, Model 1). In this respect, our results are consistent with those of previous reports. After all, weight control is the essence of the primary prevention of hypertension.

Prevention of hypertension, the most hazardous factor for cardiovascular disease, is an important public health issue. JNC VII emphasizes that subjects with an SBP of at least 120 mmHg or DBP of at least 80 mmHg are at risk for developing hypertension (*8*). Prehypertension is a useful category in which such parameters as C-reactive protein, plasma brain natriuretic peptide, or aldosterone (*35–37*) are measured to identify the subjects most likely to develop hypertension. Our previous reports demonstrated that pulse pressure and hyperuricemia were significantly associated with cardiovascular risk factors (*29*, *38*), their clustering (*38*) and the development of hypertension (*39*). Our results demonstrate that proteinuria, uric acid and pulse pressure could be other bio-measurements for identifying subjects who are at risk for this disease.

The accumulation of risk factors might have an important role in the pathogenesis of hypertension (*40*). The Framingham Heart Study group demonstrated a stepwise increase in the incidence of hypertension across the three non-hypertensive BP categories (*15*). They also demonstrated that age and obesity were risk factors for developing hypertension. Our results indicate that proteinuria is also an important risk factor for developing hypertension independent of BP levels and obesity; in fact, the OR was higher for proteinuria than for age or obesity. Therefore, a lifestyle modification program, *e.g.*, the DASH diet program, should be applied in order to prevent hypertension in subjects with a higher BP level, proteinuria, and/or obesity.

Limitations

There are some limitations to our study. First, most of the subjects were employees of companies or public organizations, or local residents who were concerned with their health. Thus, they might not be representative of the general population. This might have led to an underestimation of the incident rate of hypertension. Other social background variables, including economic status, education, and access to health information that might modify BP change, were not examined in this study.

Second, we had no information on lifestyle factors in the year 2000. As a result, we had to judge the BP status of subjects using only the BP readings themselves. This also might have led to an underestimation of the incident rate of hypertension in the present study.

Third, although BP measurement was performed twice for all subjects, only the lower values of BP data were available for the present analysis. In general, the average values should be used for analyses such as the present one, and this might have affected the subjects' BP status.

Conclusion

Proteinuria is a powerful predictor of the development of hypertension irrespective of initial age, BP level, obesity, or renal function. Weight reduction is also an important factor for the prevention of hypertension. Lifestyle modification might thus be necessary for individuals with proteinuria and/or obesity.

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