Original Article

Microalbuminuria and Cardiovascular Events in Elderly Hypertensive Patients without Previous Cardiovascular Complications

Satoko NAKAMURA, Yuhei KAWANO, Takashi INENAGA, Hajime NAKAHAMA, Takeshi HORIO, Osamu SASAKI, Naoki OKUDA^{*}, and Shuichi TAKISHITA^{**}

To assist in the development of better treatments for elderly hypertensive patients, we studied the degree to which the baseline values of urinary albumin excretion (UAE) and other cardiovascular risk factors were predictive of cardiovascular complications in a cohort of elderly hypertensive patients. In 1994, we adopted 144 elderly hypertensive patients, who had been treated for more than 6 years at various clinics and more than 1 year at the National Cardiovascular Center, Osaka, Japan. They were divided into 2 groups: a NA group ($n=111$) with normoalbuminuria ($\text{UAE} < 30 \text{ mg/day}$) and an MA group ($n=33$) with microalbuminuria ($\text{UAE } 30\text{--}300 \text{ mg/day}$). At baseline, the two groups were similar with respect to systolic and diastolic blood pressure (SBP/DBP), pulse pressure (PP), age, ratio of males to females, serum creatinine, uric acid, total cholesterol, fasting plasma glucose (FPG), and creatinine clearance (CCr). PP was calculated as SBP minus DBP. The efficacy of blood pressure (BP) control was similar in both groups during the 8-year follow up period; however, a total of 14 cardiovascular events occurred in the MA (6/33) and NA (8/111) groups, with the MA group showing the higher incidence rate by multiple logistic regression analysis ($p < 0.05$). At 8 years of follow-up, PP and age were correlated with UAE ($p < 0.05$, $p < 0.001$). At the same time point, CCr was correlated with UAE at baseline ($p < 0.05$). The results indicated that, in elderly hypertensive patients without previous cardiovascular complications, microalbuminuria can be a predictor of cardiovascular events irrespective of conventional BP control. (*Hypertens Res* 2003; 26: 603–608)

Key Words: microalbuminuria, hypertension, cardiovascular events, renal function

Introduction

It has been well established that proteinuria plays a pathophysiological role in both renal and cardiovascular diseases. In addition, it has been shown that an appreciable proportion of patients with hypertension have a greater degree of urinary albumin excretion (UAE) than normotensive subjects (1–4). In addition to severe proteinuria, microalbuminuria is

also considered to have relevance as a predictor of the progression of cardiovascular diseases (5). In diabetic subjects, microalbuminuria appears to be an important sign of early nephropathy that triggers end-stage renal disease (ESRD) and increases the incidence of cardiovascular deaths and total mortality (6). Furthermore, there is growing evidence that microalbuminuria can be used as a predictor of atherosclerosis and premature death even in non-diabetic patients and the general population (5, 7). In hypertension research, most

From the Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, Osaka, Japan, and ^{*} Department of Medicine, Sumitomo Hospital, Osaka, Japan, and ^{**} Third Department of Internal Medicine, University of Ryukyus School of Medicine, Okinawa, Japan. This study was supported by a Grant for Comprehensive Research on Aging and Health from the Ministry of Health, Labor and Welfare of Japan (H11-Comprehensive Research on Aging and Health-013).

Address for Reprints: Satoko Nakamura, M.D., Ph.D., Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, 5–7–1, Fujishiro-dai, Suita 565–8565, Japan. E-mail: snakamur@hsp.ncvc.go.jp

Received October 8, 2002; Accepted in revised form April 15, 2003.

studies on UAE have been clinical investigations into the relationship between UAE and renal insufficiency, because renal insufficiency deteriorates hypertension and *vice versa*. There is substantial evidence that a slight increase in UAE further increases the risk of ischemic heart disease in hypertensive subjects (8). Indeed, a retrospective cohort analysis has suggested that hypertensive patients with microalbuminuria manifest a greater incidence of cardiovascular events and a greater decline in renal function than hypertensive patients with normal UAE (9). Thus, blood pressure control and concomitant treatment for renal protection are important for a large majority of the population of hypertensive patients. It has been reported that good long-term control of blood pressure by conventional treatment in middle-aged hypertensive patients appears to protect the kidney from progressive decline in creatinine clearance (CCr) and increase in UAE (10). As the above evidence suggests, establishing an effective treatment for elderly hypertensive patients is another important target of research because of the complexity of the disease features in such patients. Furthermore, the pathophysiological mechanism by which microalbuminuria acts as a predictor of hypertension and related vascular and renal diseases in the elderly remains to be clarified.

A recent epidemiologic study based on the use of urine ultrafiltration indicated that there is a strong relationship between systolic and diastolic blood pressure (SBP/DBP) and microalbuminuria (11). For years, DBP has been considered a more important measurement than SBP for assessing the development of organ damage secondary to hypertension (12). Recent data suggest that pulse pressure (PP) could be a greater risk factor (13, 14). In the present study, we analyzed the findings of an 8-year follow-up analysis of elderly patients with essential hypertension without previous cardiovascular complications. The patients had been treated with antihypertensive drugs for more than 6 years, and their SBPs had been well controlled. The aim of the study was to assess the predictive impacts of microalbuminuria and blood pressure on the subsequent development of cardiovascular events and the decline of renal function in elderly hypertensive patients receiving antihypertensive therapy.

Methods

Patient Population

We conducted a prospective cohort analysis to determine whether there was an association among blood pressure, microalbuminuria, cardiovascular events, and loss of renal function in elderly patients with essential hypertension. In 1994, blood pressure, urinary albumin excretion, and other atherosclerotic risk factors were measured in 172 elderly hypertensive patients 65 years old and over, who had been treated for more than 1 year at the outpatient clinic of the National Cardiovascular Center, Osaka, Japan. A diagnosis of secondary hypertension was ruled out based on the findings

of routine blood chemistry analysis, urinalysis, and plasma renin activity and catecholamine concentration. Individuals were excluded from this analysis if they, at baseline, had cardiovascular disease (angina pectoris, myocardial infarction, or stroke), diabetes mellitus or renal disease. Angina pectoris was diagnosed by the presence of myocardial ischemia according to typical anginal symptoms or reversible ischemic changes on ECG. Myocardial infarction was diagnosed by QRS change on ECG (abnormal Q or poor R progression), hypokinesis of wall motion on echocardiogram, or elevation of serum myocardial enzyme (creatinine kinase-MB) levels. Stroke (cerebral infarction and hemorrhage) was diagnosed by the clinical history, neurological examination, and findings of computerized tomography as described elsewhere (15, 16). Diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, and/or a fasting plasma glucose (FPG) level > 126 mg/dl. Renal disease was defined from the clinical history, the presence of proteinuria, which was defined as a protein level > 1 (+) by the dye-impregnated paper strip method, and the presence of renal insufficiency, which was defined as a serum creatinine level > 1.5 mg/dl. In this manner, a total of 144 patients were selected for this study. All patients gave their informed consent to participate in this study.

With patients in the sitting position, SBP and DBP were measured 3 times with a sphygmomanometer and appropriately sized cuff, once a month throughout the follow-up period of the study. DBP was recorded at the disappearance of the Kortokoff sounds (phase V). Pulse pressure was calculated as SBP minus DBP.

Urine in patients with no sign of urinary infection was collected at 24-h periods at baseline and again after 8 years, and urine albumin excretion was measured by radioimmunoassay. Patients with hypertension were considered to have microalbuminuria if their UAE was in the range of 30–300 mg/24 h, and normoalbuminuria if their UAE was less than 30 mg/24 h. Patients were classified into two groups: a NA group with normoalbuminuria ($n = 111$) and an MA group with microalbuminuria ($n = 33$).

Weight, height, body mass index (BMI), smoking habits, fasting serum creatinine levels, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides levels, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) were obtained once a year throughout the follow-up period. CCr was calculated by measuring intrinsic creatinine in serum (SCr) and in urine. Smoking habits were obtained from the medical records.

Follow-Up

A total of 144 subjects were followed up once a month to monitor blood pressure, effectiveness of antihypertensive therapy, and prevalence of cardiovascular events. Blood pressure levels were controlled based on the fifth report of JNC V (17).

Table 1. Baseline Clinical Characteristics of Elderly Hypertensive Patients

	NA group (n = 111)	MA group (n = 33)
Age (years)	72 ± 1	73 ± 1
Male gender (%)	47 (42)	19 (58)
Height (m)	1.57 ± 0.01	1.59 ± 0.01
Weight (kg)	61.1 ± 1.0	60.9 ± 2.0
BMI (kg/m ²)	24.6 ± 0.3	24.0 ± 0.6
Duration of hypertension (years)	22 ± 1	22 ± 1
Family history of hypertension (%)	75 (68)	21 (64)
Current smokers (%)	44 (40)	18 (55)
Use of CCBs (%)	82 (74)	28 (85)
Use of ACE inhibitors (%)	25 (23)	9 (27)

NA, normoalbuminuria; MA, microalbuminuria; BMI, body mass index; CCBs, calcium channel blockers; ACE, angiotensin-converting enzyme.

In August of 2002, end points were collected from the admission records or the medical records of the outpatient to verify the diagnosis of cardiovascular and renal events and cause of death. Myocardial infarction was diagnosed using either ECG or echocardiograms, and angina pectoris was diagnosed from both symptoms and ECG. Cerebral infarction and hemorrhage were diagnosed from both neurological findings and computerized tomography. Atherosclerotic obliteration (ASO) was defined as the presence of both symptomatic claudication and an ankle/brachial pressure index less than 0.9. Dissection of the abdominal aorta was diagnosed by typical clinical history and computerized tomography findings. For all subjects who died, the cause of death was recorded.

Statistical Analysis

All analyses were performed with the program Stat-View 5.0. Differences in baseline characteristics between the groups were compared by analysis of variance (ANOVA) for continuous variables and by the χ^2 test for categorical variables. Values of $p < 0.05$ were considered to indicate statistical significance. Survival during the follow-up period was calculated by Kaplan-Meier curves for different groups and differences were tested by the log rank test. Relationships between UAE or CCr at 8-year follow-up and other clinical characteristics were evaluated using linear regression analysis. Cox proportional hazard regression analysis was performed to examine the relationship between cardiovascular events and several cardiovascular risk factors, *i.e.*, age, gender, smoking, BMI, DBP, PP, uric acid, total cholesterol, FPG, CCr, and UAE. Results are described as relative risks (RRs) (hazards ratio) with 95% confidence intervals (CIs). The results are expressed as the means ± SEM.

Results

Table 1 shows the baseline clinical characteristics of the two groups of patients. Age, gender, BMI, duration of hypertension, family history of hypertension, and smoking status did not differ significantly between groups. The use of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) also did not differ significantly. Although treatments with antihypertensive drugs throughout the follow-up period changed occasionally, the total number of prescriptions for ACE inhibitors and CCBs did not change substantially between groups in either group. Table 2 shows the clinical characteristics at baseline and at the 8-year follow-up for both groups. Blood pressure was not different between groups at either measurement. Creatinine concentrations of the MA group at baseline and at the 8-year follow-up were greater than those in the NA group ($p < 0.005$). UAE values (as defined above) in the MA group at baseline and at the 8-year follow-up were greater than those in the NA group ($p < 0.0001$). CCr in the MA group at the 8-year follow-up was lower than that in the NA group ($p < 0.01$). Serum levels of uric acid, total cholesterol, triglycerides, FPG, and HbA1c did not differ significantly. Table 2 also shows the differences in UAE and CCr between the baseline and 8-year follow-up period. UAE increased in both groups ($p < 0.05$). CCr decreased in both groups ($p < 0.05$). The decline of CCr from baseline to 8-year follow-up in the MA group was significantly greater than that in the NA group ($p < 0.05$).

Table 3 shows the relationships between UAE at the 8-year follow-up and other clinical characteristics. The relationships between UAE at the 8-year follow-up and each of age, SBP at 8-year follow-up, DBP at baseline, PP, UAE at baseline, and CCr were significantly positive in linear regression analysis. Table 4 shows the relationships between CCr at the 8-year follow-up and other clinical characteristics. Linear regression analysis showed that age, UAE, DBP at baseline, and CCr at baseline were significantly correlated to CCr at the 8-year follow-up.

The incidence of cardiovascular events was significantly greater in the MA group than in the NA group ($p < 0.05$) (Fig. 1). At the 8-year follow-up, 6 of 33 patients (18%) in the MA group had experienced major cardiovascular events: one had acute myocardial infarctions, three had cerebral infarction, and two had dissection of the abdominal aorta. In the NA group, 8 of 111 patients (7%) experienced major cardiovascular events: one had acute myocardial infarctions, two had angina pectoris, one had cerebral infarction, three had cerebral hemorrhage (one fatal), and one had atherosclerotic obliteration (Table 5). Two patients in the MA group died due to colon cancer; these deaths were not cardiovascular in origin. Cox proportional hazard regression analysis showed that UAE at baseline was related to the incidence of cardiovascular events (Table 6).

Table 2. Clinical Characteristics of Elderly Hypertensive Patients

		NA group	MA group	<i>p</i>
SBP (mmHg)	Baseline	144 ± 1	145 ± 3	0.83
	8-year follow-up	143 ± 1	142 ± 3	0.93
DBP (mmHg)	Baseline	84 ± 1	85 ± 1	0.56
	8-year follow-up	81 ± 1	81 ± 1	0.98
PP (mmHg)	Baseline	60 ± 1	60 ± 3	0.83
	8-year follow-up	61 ± 1	61 ± 3	0.93
Creatinine (mg/dl)	Baseline	0.78 ± 0.02	0.91 ± 0.05	< 0.005
	8-year follow-up	0.73 ± 0.02	0.90 ± 0.07	< 0.005
Uric acid (mg/dl)	Baseline	5.6 ± 0.1	5.9 ± 0.2	0.29
	8-year follow-up	5.7 ± 0.1	5.9 ± 0.2	0.44
UAE (mg/24 h)	Baseline	13 ± 1	92 ± 11	< 0.0001
	8-year follow-up	25 ± 4 [#]	200 ± 60 [#]	< 0.0001
CCr (ml/min)	Baseline	93.8 ± 2.3	89.8 ± 4.4	0.46
	8-year follow-up	73.4 ± 2.1 [#]	60.6 ± 4.2 [#]	< 0.01
Total cholesterol (mg/dl)	Baseline	203 ± 3	192 ± 5	0.08
	8-year follow-up	205 ± 3	203 ± 4	0.62
Triglycerides (mg/dl)	Baseline	132 ± 7	152 ± 15	0.21
	8-year follow-up	133 ± 6	162 ± 21	0.08
HDL-cholesterol (mg/dl)	Baseline	56 ± 2	52 ± 3	0.39
	8-year follow-up	52 ± 2	48 ± 2	0.20
FPG (mg/dl)	Baseline	101 ± 1	105 ± 2	0.08
	8-year follow-up	104 ± 2	105 ± 2	0.52
HbA1c (%)	Baseline	5.6 ± 0.1	5.7 ± 0.2	0.77
	8-year follow-up	5.5 ± 0.1	5.6 ± 0.1	0.83

NA, normoalbuminuria; MA, microalbuminuria, SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; UAE, urinary albumin excretion; CCr, creatinine clearance; HDL, high-density lipoprotein; FPG, fasting plasma glucose. [#] *p* < 0.05 vs. baseline.

Table 3. Relationships between UAE at 8-Year Follow-Up and Other Clinical Characteristics

Variables	<i>r</i>	<i>p</i>
Age	0.30	< 0.001
SBP at baseline	0.11	0.21
SBP at 8-year follow-up	0.14	< 0.05
DBP at baseline	0.16	< 0.05
DBP at 8-year follow-up	0.13	0.12
PP at baseline	0.19	< 0.05
PP at 8-year follow-up	0.22	< 0.01
UAE at baseline	0.33	< 0.0001
CCr at baseline	0.17	< 0.05
CCr at 8-year follow-up	0.20	< 0.05

Definitions are as Table 2.

Table 4. Relationships between Creatinine Clearance at 8-Year Follow-Up and Other Clinical Characteristics

Variables	<i>r</i>	<i>p</i>
Age	0.33	< 0.0001
SBP at baseline	0.08	0.31
SBP at 8-year follow-up	0.01	0.95
DBP at baseline	0.27	< 0.05
DBP at 8-year follow-up	0.13	0.12
PP at baseline	0.05	0.53
PP at 8-year follow-up	0.08	0.34
UAE at baseline	0.20	< 0.05
UAE at 8-year follow-up	0.20	< 0.05
CCr at baseline	0.45	< 0.0001

Definitions are as Table 2.

Discussion

In Japan, hypertension has been shown to be a significant predictor of stroke, myocardial infarction, and ESRD (18, 19). Arguments have been made as to whether microalbuminuria can predict the prognosis of hypertensive patients. One retrospective study reported a greater incidence of stroke and other cardiovascular events in non-diabetic elderly subjects with increased UAE than in those with normal UAE (20). A recent prospective study showed that microalbuminuria was an independent risk factor of cardiovascular and all-cause mor-

talidity, especially among hypertensive subjects (21). However, in elderly hypertensive patients with microalbuminuria, prediction of prognosis in clinical practice is difficult because of the complexity of the features of the disease. Thus, whether microalbuminuria is a strong marker for potential progression of disease and/or eventually emerging cardiovascular events remains to be investigated.

The present study dealing with 144 hypertensive patients aged 65 years or older without previous cardiovascular complications revealed that patients manifesting microalbuminuria at baseline (MA group) had a higher incidence (6/33:18.2%) of cardiovascular events than those with nor-

Fig. 1. Cardiovascular event-free survival curves for elderly hypertensive patients with microalbuminuria (MA group: closed square) and patients without microalbuminuria (NA group: open circle). The difference between the two groups was significant in terms of the Kaplan-Meier survival curves and by log rank test ($p < 0.05$).

Table 5. Cardiovascular Events in Elderly Hypertensive Patients with and without Microalbuminuria

Events	NA group ($n = 111$)	MA group ($n = 33$)
Myocardial infarction	1	1
Angina pectoris	2	0
Cerebral infarction	1	3
Cerebral hemorrhage	3	0
Arteriosclerosis obliteration	1	0
Dissection of abdominal aorta	0	2
Total	8	6

Definition are as Table 2.

microalbuminuria (NA group) (8/111: 7.2%) during the 8-year follow-up period. The degree of UAE at the 8-year time point was closely related to UAE at baseline as well as to the age of patients, SBP at 8-year follow-up, DBP at baseline, and PP at baseline, indicating that microalbuminuria was not restored despite the therapeutic blood pressure control. Thus, microalbuminuria at baseline reflected the cardiovascular and renal events as endpoints during the 8-year follow up. Indeed, the CCr levels at baseline were related to the CCr levels at 8 years as well as to the age of patients and DBP at baseline (Table 4). UAE at baseline and UAE at 8 years were significantly correlated with CCr at 8 years, indicating that, in elderly hypertensive patients, mild renal impairment was retained during throughout the follow-up period. As shown in Table 6, cardiovascular events emerging during the 8-year period were closely correlated with the degree of UAE at baseline, as revealed by Cox proportional hazard regression analysis. Other risk factors, such as advanced age, gender, obesity, smoking, DBP, PP, CCr, dyslipidemia, and FPG, were not significantly related with cardiovascular

Table 6. Relative Risks by Cox Proportional Hazard Regression Analysis of 8-Year Cardiovascular Events Associated with Potential Risk Factors

Risk factors	Relative risk (95% CI)	p
Age at baseline	1.10 (0.92–1.24)	0.37
Gender (male)	2.93 (0.61–14.04)	0.18
BMI	0.96 (0.76–1.21)	0.71
Current smokers	2.25 (0.45–11.15)	0.32
DBP at baseline	0.94 (0.84–1.05)	0.24
PP at baseline	1.00 (0.95–1.05)	0.91
UAE at baseline	1.10 (1.00–1.20)	< 0.005
CCr at baseline	1.02 (0.99–1.05)	0.11
FPG at baseline	0.97 (0.91–1.03)	0.32
T-chol at baseline	1.00 (0.98–1.03)	0.67

T-chol, total cholesterol. Other definitions are as Table 2.

events.

Several factors are thought to be involved in the mechanism of elevated UAE, including renal hemodynamic changes with increased intraglomerular pressure, changes in perm selectivity of the glomerular filter due to structural changes in glomerular tufts that are often associated with nephrosclerosis, and so on (3). All these factors are known to be associated with high blood pressure, and high blood pressure can affect renal function through functional and morphological changes of nephrons. Thus, proteinuria is a crucial factor for the pathogenesis of hypertension and renal insufficiency.

Numerous studies have provided evidence of a relationship between microalbuminuria and hypertension. In several studies on non-diabetic hypertensive subjects, the prevalence of microalbuminuria has been reported to be 20% to 40% or more, and UAE has been shown to be increased with age and with severity and duration of hypertension (22). Other studies have shown a significant correlation between UAE and office blood pressure values (11, 23), continuous ambulatory blood pressure measurements (24), or PP (25). In our present study patients whose averaged age was 72.7 years at baseline had been treated for more than 6 years, and their blood pressure was well controlled, at least during the successive 8-year follow-up period. Pulse pressure showed a positive relationship to UAE at the 8-year follow-up. The prevalence of microalbuminuria was almost 25% at baseline, and 41% at the 8-year follow-up, showing almost same percentage as described with the both percentages being almost identical to those described in the previous report (22). The elderly hypertensive patients adopted in the present study were thus general. Nonetheless, the occurrence of cardiovascular events was higher in the group having microalbuminuria at baseline, independent of their blood pressure control.

Our present study did not indicate a positive relation between smoking and cardiovascular events. Again, gender, lipid metabolism, and FPG were not correlated with cardio-

vascular events. However, we do not conclude that all these parameters have little relevance to cardiovascular events and prognosis of elderly hypertensive patients, because in the present study the total number of patients in the MA group was about 1/3 of that in the NA group, and thus there may have been an unexpected, underlying bias. Further investigation is therefore necessary with a larger number of patients and a longer period of follow up.

In conclusion, in the present study elderly hypertensive patients without previous cardiovascular complications, whose risks (except smoking) were not very high (no diabetes mellitus, and blood pressure was controlled) but who had microalbuminuria, manifested a greater incidence of cardiovascular events and a greater decline in renal function than those with normoalbuminuria in an 8-year follow up. Although the mechanism by which microalbuminuria influences the prognosis of hypertension in the elderly population is unclear, microalbuminuria might more properly express already existing microvascular lesions than serum cholesterol or glucose levels. Microalbuminuria may be a good of cardiovascular events in elderly hypertensive patients receiving long-term conventional antihypertensive therapy. Our results suggest that UAE measurements should be considered as an important adjunct to the evaluation of elderly patients with essential hypertension.

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