Distribution Pattern of Urine Albumin Creatinine Ratio and the Prevalence of High-Normal Levels in Untreated Asymptomatic Non-Diabetic Hypertensive Patients

Natsuki Ohmaru¹, Takaaki Nakatsu², Reishi Izumi¹, Keiichi Mashima², Misako Toki², Asako Kobayashi², Hiroko Ogawa³, Satoshi Hirohata¹, Satoru Ikeda¹ and Shozo Kusachi¹

Abstract

Background Even high-normal albuminuria is reportedly associated with cardiovascular events.
Objective We determined the urine albumin creatinine ratio (UACR) in spot urine samples and analyzed the UACR distribution and the prevalence of high-normal levels.
Patients and Methods The UACR was determined using immunoturbidimetry in 332 untreated asymptomatic non-diabetic Japanese patients with hypertension and in 69 control subjects. The microalbuminuria and macroalbuminuria levels were defined as a UACR \( \geq 30 \) and \(< 300 \, \mu g/\text{mg}\, \text{creatinine} \) and a UACR \( \geq 300 \, \mu g/\text{mg}\, \text{creatinine} \), respectively.
Results The distribution patterns showed a highly skewed distribution for the lower levels, and a common logarithmic transformation produced a close fit to a Gaussian distribution with median, 25th and 75th percentile values of 22.6, 13.5 and 48.2 \( \mu g/\text{mg}\, \text{creatinine} \), respectively. When a high-normal UACR was set at >20 to <30 \( \mu g/\text{mg}\, \text{creatinine} \), 19.9\% (66/332) of the hypertensive patients exhibited a high-normal UACR. Microalbuminuria and macroalbuminuria were observed in 36.1\% (120/336) and 2.1\% (7/332) of the patients, respectively. UACR was significantly correlated with the systolic and diastolic blood pressures and the pulse pressure. A stepwise multivariate analysis revealed that these pressures as well as age were independent factors that increased UACR.
Conclusion The UACR distribution exhibited a highly skewed pattern, with approximately 60\% of untreated, non-diabetic hypertensive patients exhibiting a high-normal or larger UACR. Both hypertension and age are independent risk factors that increase the UACR. The present study indicated that a considerable percentage of patients require anti-hypertensive drugs with antiproteinuric effects at the start of treatment.

Key words: blood pressure, kidney, proteinuria, albumin, risk factor

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Introduction

In patients with essential hypertension, an elevated urinary albumin excretion level below the proteinuric level, i.e., microalbuminuria, has been shown to be an early sign of glomerular disease (1). Microalbuminuria is reportedly associated with an increased cardiovascular risk regardless of the presence of diabetes (2, 3). The early detection and correction of microalbuminuria is thought to be important for preventing the deterioration of renal function and for reducing cardiovascular events (4, 5).

Several recent studies have indicated that even high-normal levels of urinary albumin excretion (UAE) (below the level suggesting microalbuminuria) are associated with an increased mortality and risk of cardiovascular events (6-9). Although several studies have examined the prevalence of microalbuminuria in untreated non-diabetic

¹Department of Medical Technology, Okayama University Graduate School of Health Sciences, Japan and ²Department of Cardiology, Kagawa-ken Saiseikai Hospital, Japan

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Correspondence to Dr. Shozo Kusachi, sh-ksc56@oninet.ne.jp
to the 1999 World Health Organization-International Society previously. Essential hypertension was diagnosed according to the criteria of Hypertension Guidelines for the management of hypertension (13). Hypertension was defined as a systolic blood pressure (sBP) ≥140 mmHg and/or a diastolic blood pressure (dBP) ≥90 mmHg on at least two measurements performed in a medical office. Both the hypertensive patients and the control subjects underwent their first medical examination at the time of their first visit to our hospital. None of the participants had previously received any pharmaceutical treatment. The exclusion criteria were as follows: 1) liver dysfunction, 2) patients with heart failure (New York Heart Association functional class ≥ II), and 3) the presence of cerebrovascular disease, coronary artery disease, cardiomyopathy, or arrhythmia. Liver dysfunction was defined as abnormally elevated serum markers for liver function observed during routine laboratory tests performed at the time of the first visit. Non-association of cerebrovascular disease, coronary artery disease, cardiomyopathy, or arrhythmia was determined based on the patient’s history, symptoms and physical examinations. Diabetes mellitus was diagnosed according to the guidelines of the Japanese Diabetic Society. Similarly, hyperlipidemia was diagnosed according to the guidelines of the Japan Atherosclerosis Society (14). Finally, 332 consecutive non-diabetic asymptomatic hypertensive patients were analyzed. The control subjects were outpatients with indefinite complaints in whom no clinically meaningful medical disorders were identified. The clinical characteristics of the patients and the control subjects are listed in Table 1. The study protocol complied with the rules of the Helsinki Declaration and was approved by our institution’s ethics committee for human research (15).

**Patients and Methods**

**Patients**

We measured the urinary albumin concentrations in control subjects and non-diabetic Japanese outpatients with asymptomatic essential hypertension who had not been treated previously. Essential hypertension was diagnosed according to the 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension (13). Hypertension was defined as a systolic blood pressure (sBP) ≥140 mmHg and/or a diastolic blood pressure (dBP) ≥90 mmHg on at least two measurements performed in a medical office. Both the hypertensive patients and the control subjects underwent their first medical examination at the time of their first visit to our hospital. None of the participants had previously received any pharmaceutical treatment. The exclusion criteria were as follows: 1) liver dysfunction, 2) patients with heart failure (New York Heart Association functional class ≥ II), and 3) the presence of cerebrovascular disease, coronary artery disease, cardiomyopathy, or arrhythmia. Liver dysfunction was defined as abnormally elevated serum markers for liver function observed during routine laboratory tests performed at the time of the first visit. Non-association of cerebrovascular disease, coronary artery disease, cardiomyopathy, or arrhythmia was determined based on the patient’s history, symptoms and physical examinations. Diabetes mellitus was diagnosed according to the guidelines of the Japanese Diabetic Society. Similarly, hyperlipidemia was diagnosed according to the guidelines of the Japan Atherosclerosis Society (14). Finally, 332 consecutive non-diabetic asymptomatic hypertensive patients were analyzed. The control subjects were outpatients with indefinite complaints in whom no clinically meaningful medical disorders were identified. The clinical characteristics of the patients and the control subjects are listed in Table 1. The study protocol complied with the rules of the Helsinki Declaration and was approved by our institution’s ethics committee for human research (15).

**Microalbuminuria**

The urine albumin creatinine ratio (UACR) was calculated using a single spot urine specimen collected in the morning. The urine albumin concentration was determined using immunoturbidimetry with automatic immunoassay equipment and a reagent kit (Lanpia, ALB-UR; Kyokutou Pharmaceutical Industrial Co., Ltd., Takahagi, Japan) that included gout anti-human albumin antibodies. The intra-assay and inter-assay coefficients of variation in the automated assay system were less than 5%. The linearity for the albumin measurements in this assay system extended from 0 to 200 mg/L. Microalbuminuria and macroalbuminuria were defined as a UACR ≥30 and <300 μg/mg·creatinine and a UACR ≥300 μg/mg·creatinine, respectively, according to the criteria of the National Kidney Foundation (16). In the present study, the lower threshold for the high-normal UACR range was set at two-thirds of the lower limit of microalbuminuria,

<table>
<thead>
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<th>Table 1. Characteristics of Participant in the Study</th>
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</tr>
<tr>
<td>DBP mmHg</td>
</tr>
<tr>
<td>PP mmHg</td>
</tr>
<tr>
<td>HR beats/min</td>
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</table>

UACR, urine albumin creatinine ratio; BMI, body mass index; T.CHO, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

hypertensive patients (10) and a wide range of prevalence rates from 4-46% have been reported, no reports have focused on the prevalence of high-normal UAE. Two studies have indicated racial differences in the prevalence of microalbuminuria (11, 12). Accordingly, we examined the distribution of the urine albumin creatinine ratio (UACR) and the prevalence of high-normal levels in untreated asymptomatic non-diabetic Japanese patients with essential hypertension.
based on previously reported findings (7, 8). Consequently, the high-normal range of UACR was defined as >20 to <30 μg/mg-creatinine.

**Serum measurements**

Serum lipid levels (total cholesterol [TC], high density lipoprotein cholesterol [HDL-C], and triglyceride [TG]) were measured using automated enzymatic methods at each facility (17). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation (18, 19). To exclude patients with diabetes mellitus, the hemoglobin A1c (HbA1c) level was measured using well-established methods and high-performance liquid chromatography with an appropriate gel column and an automated analyzer (20, 21).

**Statistics**

The data were analyzed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL). The UACR distributions were examined using the Kolmogorov-Smirnov test. Logarithmically transformed UACR values were also analyzed (22). Data were expressed as the median and 25th and 75th percentiles. To compare the baseline characteristics of the patients and the control subjects, we used the Mann-Whitney U-test and the Chi-square test to analyze continuous and categorical variables, respectively. The Kruskal-Wallis test with Bonferroni correction was used to compare data among more than three groups. A simple correlation analysis was performed to assess the relationship between the UACR and the blood pressure as well as other factors. A stepwise multiple linear regression analysis was also performed, using UACR as the dependent variable. Several studies have reported a relation between urine albumin excretion and the risk factors for atherosclerosis (23, 24). Therefore, we selected age, sex, and risk factors for arteriosclerosis; body mass index, serum LDL-C and triglyceride levels, smoking habits, and BPs (sBP, dBP and pulse pressure) as independent variables. The multicollinearity of among the factors was assessed by evaluating variance inflation factors. Probability values of less than 0.05 were considered significant.

**Results**

**Clinical backgrounds**

Table 1 summarizes the clinical backgrounds of the patients and control subjects. Among the hypertensive patients, 45%, 35%, and 35% had obesity, dyslipidemia, and a smoking habit, respectively. The age of the hypertensive patients was approximately 10 years older than that of the control subjects. The body mass index was slightly but significantly higher among the hypertensive patients than among the control subjects. The serum cholesterol levels and smoking habits were not significantly different between the patients and control subjects. The serum TG level was slightly higher among the hypertensive patients. Although the serum creatinine levels were in the normal ranges, slightly higher serum creatinine levels were observed in the hypertensive patients than in the control subjects.

**Prevalence and extent of microalbuminuria**

As shown in Fig. 1, the UACR distribution was highly skewed to the left side (lower levels), resulting in the absence of a Gaussian distribution. A common logarithmic transformation of the UACR produced a distribution that was close to a Gaussian distribution, though the distribution did not reach a statistically significant fit as judged using the Kolmogorov-Smirnov test. Positive coefficients for skewness (0.496) and high kurtosis (1.553) indicated that the log UACR distribution was shifted to the left side and a higher peak, compared with a normal distribution pattern. The median, 25th and 75th percentile values were 22.6, 13.5 and 48.2 μg/mg-creatinine, respectively. In hypertensive patients with UACR levels below the threshold for microalbuminuria, the cutoff values for the quartile distribution were 11.6, 15.4 and 21.1 μg/mg-creatinine, respectively (n=50, 51, 51 and 53, respectively). The median value was 15.4 μg/mg-creatinine. When the lower limit of the UACR for the high-normal range of UACR was set at 20 μg/mg-creatinine (7, 8), which was two-thirds of the lower limit for microalbuminuria and close to the cutoff value between the 3rd and 4th quartiles, 19.8% (66/332) of the patients were classified as having a high-normal UACR (Fig. 2). One-third of the patients exhibited microalbuminuria (36.1%, 120/332). When the median UACR value (15.4 μg/mg-creatinine), which was half of the lower threshold for microalbuminuria (6), was used as the lower limit of the high-normal range of UACR, 31.6% (105/332) of the hypertensive patients were classified as having a high-normal UACR. The prevalence of patients with UACR values falling within the normal (<30 μg/mg-creatinine) and macroalbuminuria ranges (≥300 μg/mg-creatinine) was 61.7% (205/332) and 2.1% (7/332), respectively. When the UACR of the patients was compared with that of the control subjects, the prevalence of microalbuminuria among the control subjects was very low (2.8%, 2/69). A high-normal UACR was observed in 8.7% (6/69) of the control subjects. The 75th, 90th and 99th percentiles of the UACR distribution among the control subjects were 15.3, 23.9 and 30.1 μg/mg-creatinine. The UACR at the 99th percentile agreed well with the lower limit for microalbuminuria according to the criteria of the National Kidney Foundation (16).

**Correlation with BP and other Factors**

The sBP, dBP and pulse pressure were significantly correlated with UACR not only among the participants overall, but also among the hypertensive patients (Fig. 3). A simple correlation indicated that UACR was correlated with age among all the patients and among the hypertensive patients (r=0.304, r=0.208, respectively; p<0.001). Although the serum creatine levels were distributed within the normal range, the levels were significantly but very weakly correlated with
Figure 1. Distribution of urine albumin creatinine ratio (UACR). Upper left and right, UACR and common logarithmically transformed UACR, respectively, for hypertensive patients. Lower left and right panels, UACR and common log-transformed UACR, respectively, for control subjects.

UACR among all the participants and among the hypertensive patients (r=0.014 and 0.023, respectively; p<0.01). The other factors were not correlated with the UACR and were not different among the hypertensive patients with UACR values corresponding to the normal, high-normal, microalbuminuria and macroalbuminuria categories (Table 2).

Multivariate analysis

A stepwise multivariate linear regression analysis that included several essential independent factors, as noted in the Statistics section, selected sBP, dBP and pulse pressure as well as age as independent factors associated with an increase in the urinary excretion of albumin among all the participants and among the hypertensive patients (Table 3). Multicollinearity among the selected factors was not observed when variance inflation factors were evaluated.

Discussion

The present study clarified that approximately 60% of untreated, asymptomatic, non-diabetic Japanese hypertensive patients had a high-normal or greater UACR. Hypertension and age were significant independent factors associated with an increased UACR in these patients. Twenty-four-hour urine collection is rather difficult for outpatients to perform. Accordingly, we used “spot” urine collected in the morning. The UACR of “spot” urine collected in the morning accurately predicts the 24-hour urinary albumin excretion (16). The adequateness of the use of spot urine for the evaluation of the urinary excretion of albumin has been reviewed (25, 26). Similar applications using spot urine have been reported in other studies (27). The validity of the immunoturbidimetry method has been well established (28), with the same cutoff value of 30 μg/mg-creatinine (16, 29). Thus, the present analytical methods seem valid, and the results can be discussed with reference to the previously reported results.

The clinical cutoff level for high-normal UACR has not yet been established. A previous study found that diabetic patients with a UACR > two-thirds of the lower limit of the microalbuminuria range had a significantly higher cardiovascular risk than patients with a UACR ≤ two-thirds of the lower limit (8). Another study categorizing patients with UACR values below the microalbuminuria levels according to the quartile values reported that patients in the highest quartile had more adverse cardiovascular and metabolic risk profiles than those in the bottom three-fourths among hypertensive men (7). As described in the Results section, two-thirds of the lower limit of the UACR corresponded to 20 μg/mg-creatinine, and the UACR threshold between the 3rd and 4th quartiles in the present study was 21.1 μg/mg-creatinine. A similar threshold has been reported for middle-aged non-diabetic subjects (30). On the other hand, among the type 2 diabetic patients with a UAE level below the microalbuminuria range, those with a higher than median UAE showed a higher incidence of micro- and macroalbuminuria.
The median UACR level in the present patients with UACR below the microalbuminuria level was 15.4 μg/mg·creatinine, which was just half of the lower UACR limit for microalbuminuria in the present study. Half the lower level for microalbuminuria was used in a previous review article (6). Another recent meta-analysis (31) suggested that a value of 10 μg/mg·creatinine be used as a threshold for an increase in cardiovascular events and death. This meta-analysis included patients with diabetes mellitus. While a multivariate analysis was used to adjust the results for the effects of diabetes mellitus, the results of the meta-analysis cannot be directly compared with the present results. When a value of 10 μg/mg·creatinine was used as the lower limit of the high-normal range, 52% of the patients exhibited a high-normal UACR. On the other hand, population-based studies have suggested even lower threshold levels of UACR for microalbuminuria (2, 32). One of these studies used urine samples that had been stored for 11-12 years and the range of the urine albumin distribution was extremely narrow, while the other study examined patients with a history of cardiovascular and/or cerebrovascular disease. Thus, the thresholds indicated by these studies may not be applicable to the present study. Although the UACR is a continuous variable affecting the prevalence of cardiac events, these considerations indicated that a threshold of 15 or 20 μg/mg·creatinine was clinically appropriate as the lower limit of the high-normal UACR range.

We found that the UACR distribution was highly skewed toward lower levels, resulting in approximately 30% and 35% of the patients having high-normal and microalbuminuria levels of UACR, respectively. No previous reports have analyzed the distribution of UACR and the prevalence of high-normal UACR values; therefore, the present results cannot be compared with previous studies. However, several studies have examined the prevalence of microalbuminuria in hypertensive patients ever since the association of microalbuminuria with non-diabetic hypertension was first reported by Parving et al (33). The reported prevalence of microalbuminuria has ranged from 4-40% (10, 34). The reason for this wide range in prevalence can be explained by differences in the urine albumin measurement methods and the different definitions of microalbuminuria that were used. In the five most recent studies, a prevalence of microalbuminuria of 32-46% was reported, similar to the results of the present study (23, 35-38). Another study examining hypertensive Japanese patients, including patients with diabetes, reported a prevalence of microalbuminuria of 27%, which was lower than that in the present study (39). The reason for this difference is uncertain. The previous study was a multi-center cohort study, and the ages of the patients were slightly lower than those in the present study. This difference may account for the difference in the prevalence of microalbuminuria between this previous study and the present study. Overall, the present results indicated that a considerable number of Japanese hypertensive patients had microalbuminuria despite being asymptomatic and non-diabetic.
Two previous studies have discussed racial differences in the prevalence of microalbuminuria (11, 12). However, neither of these studies examined the prevalence of microalbuminuria among Asians. Although one of the studies (11) was a cohort study from Boston and did not focus on hypertensive patients, slight differences in the prevalence of microalbuminuria between non-Hispanic white and non-Hispanic black populations were reported. Another study examining hypertensive patients reported a higher prevalence of microalbuminuria among black hypertensive patients than among white hypertensive patients (32% vs. 14%). The prevalence observed in the present study was compatible with five recent studies from Italy and Spain (23, 35-38). Thus, the present results showed that the prevalence of microalbuminuria among hypertensive Japanese patients was similar to that among Western patients.

A multivariate analysis demonstrated that both hypertension and age were independent factors associated with an increase in urine albumin excretion. Factors in addition to age and those that promote atherosclerosis are also likely correlated with the extent of microalbuminuria. Conflicting results have been reported regarding the relationship between risk factors for atherosclerosis and microalbuminuria (24, 34). At present, no study has found a clear relationship between any of these factors and microalbuminuria. The present results agreed well with the previously reported findings. Overall, the present analyses indicated that among the risk factors for atherosclerosis, hypertension is likely to be a strong factor that increases the UACR.

Many studies, including the HOPE study, have demonstrated a significant relationship between microalbuminuria and the risk of cardiovascular disease (1-3, 7, 8, 40). All these studies emphasized that high-normal levels of UACR were associated with a clinically significant risk of cardiovascular disease, indicating the importance of determining the UACR. The UACR distribution pattern observed in the present study clarified that a considerable number of untreated hypertensive patients have high-normal UACR and require microalbuminuria-reduction therapy. Previous studies have examined the reduction in microalbuminuria using drugs in hypertensive patients (41-44). In addition to studies on microalbuminuria reduction, however, studies focusing on the reduction of normal to high-normal UACR values using drugs are also important. Our recent study clearly demonstrated that cilnidipine, an L- and N-type calcium channel blocker, reduced not only microalbuminuria but also normal to high-normal UACR values using drugs are also important. Our recent study clearly demonstrated that cilnidipine, an L- and N-type calcium channel blocker, reduced not only microalbuminuria but also normal to high-normal UACR (45). Further studies on high-normal UACR reduction using various series of drugs are essential. The present results indicate that a considerable proportion of untreated hypertensive patients have a high-normal UACR and require appropriate medication for the reduction of these low levels of albuminuria at the time of their initial visit to an outpatient clinic.

The present study has several limitations. First, a relatively small number of subjects were examined. However, the number of patients in several recent studies reporting a similar prevalence of microalbuminuria among hypertensive patient was similar to that in the present study (23, 37, 38). Among our control subjects, the 99th percentile of the UACR distribution was identical to the lower limit of microalbuminuria according to the National Kidney Foundation criteria (16). Furthermore, the data distribution was not ir-
Table 2. Comparison of Patient Characteristics among Hypertensive Patients with Different UACR Levels

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<th>C: 30≤UACR≤300</th>
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<td>68.2</td>
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UACR, urine albumin creatinine ratio; BMI, body mass index; T.CHO, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure

Table 3. Results of Stepwise Multiple Linear Regression Analysis

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regular, but rather it resembled a Gaussian pattern, indicating that the patients studied were not exceptional cases but were representative of a large cohort of non-diabetic, asymptomatic hypertensive Japanese patients. These considerations suggest that the number of patients in the present study was sufficient. A study involving a larger number of patients is, however, required to confirm the results of the present study. Second, the age of the control group was not matched with that in the patient group. Careful statistical analysis using a multivariate analysis may at least partly compensate for this limitation.

In conclusion, the present study clarified that a substantial percentage of Japanese untreated non-diabetic hypertensive patients exhibited a high-normal and larger UACR, even though the patients were asymptomatic. Anti-proteinuria therapy may be required in a large proportion of hypertensive patients beginning at the start of their initial therapy.

The authors state that they have no Conflict of Interest (COI).
References


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