Comparison of Microalbuminuria in 2 Blood Pressure Categories of Prehypertensive Subjects

Byung Jin Kim, MD, PhD*; Hyun Jong Lee, MD*; Ki Chul Sung, MD, PhD; Bum Soo Kim, MD, PhD; Jin Ho Kang, MD, PhD; Man Ho Lee, MD, PhD; Jung Ro Park, MD, PhD

Background Subjects with high normal blood pressure (BP: systolic, 130–139 mmHg or diastolic, 85–89 mmHg) have higher cardiovascular risks compared with individuals with normal BP (systolic BP, 120–129 mmHg or diastolic BP, 80–84 mmHg). In the present study the prevalence of microalbuminuria and cardiovascular risk factors, as well as factors that influence microalbuminuria, were assessed in 2 groups of subjects with prehypertension.

Methods and Results Of 2,678 prehypertensive subjects (1,689 men, 989 women), none had a history of diabetes or hypertension. Urine albumin excretion was measured by an immunoradiometric assay in a morning urine sample. The prevalence of microalbuminuria in the high normal BP group was higher than in the normal BP group (4.9% vs 2.8%, p=0.009). Subjects with high normal BP were older, and had higher prevalence of males and metabolic syndrome; larger waist circumference and body mass index, higher levels of triglycerides, fasting blood glucose, uric acid and ferritin, and lower levels of high-density lipoprotein-cholesterol were more common in subjects with high normal BP than in those with normal BP. Multiple logistic regression analysis showed that the high normal BP category had an independently significant association with microalbuminuria (odds ratio = 1.692, 95% confidence interval 1.097–2.611).

Conclusions Subjects with high normal BP have greater risk factors for cardiovascular disease, including microalbuminuria, than those with normal BP. Further investigations are needed to ascertain whether more positive treatment strategies for the early prevention of cardiovascular disease might be needed for individuals with high normal BP.

Key Words: Albuminuria; Cardiovascular diseases; Hypertension

The Framingham Heart Study has indicated that individuals with high normal BP (SBP 130–139 mmHg or DBP 85–89 mmHg) have a more than 2-fold increase in relative risk for cardiovascular disease compared with those who have optimal BP.

Other previous studies have reported that individuals with high normal BP have a higher rate of progression to hypertension and odds ratio (OR) for hypertension, compared with those with normal BP (SBP 120–129 mmHg, DBP 80–84 mmHg).

However, epidemiologic data on the relationship between the 2 BP categories of prehypertension and cardiovascular risk factors, including microalbuminuria, is limited, especially in Asian populations. Microalbuminuria is a useful biological marker of individuals who are at high risk for cardiovascular events and who require more intensive therapy. Therefore, we compared the prevalence of microalbuminuria and other cardiovascular risk factors in 2 groups of prehypertensive subjects, none of whom had a past history of diabetes or hypertension. In addition, we assessed the factors influencing microalbuminuria, and whether the BP category might be independently associated with the presence of microalbuminuria.

Methods

Study Population A total of 76,973 subjects underwent a baseline examination at the health promotion center of Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

*Byung Jin Kim and Hyun Jong Lee have contributed equally to the work reported and both should be considered as first authors.
Hospital between January and December 2005. Of these, after excluding the following criteria, 2,678 prehypertensive subjects (1,689 men, 989 women) were included for this study. The exclusion criteria were: (1) previously diagnosed or newly diagnosed with diabetes, hypertension or other cardiovascular diseases, (2) renal diseases including renal parenchymal diseases or renal insufficiency (serum creatinine >123.8 μmol/L and 106.1 μmol/L in men and women, respectively), and (3) acute inflammatory diseases, thyroid diseases, malignant tumors and overt proteinuria. The study was approved by the Ethical Committee of Kangbuk Samsung Hospital and all patients gave written informed consent.

Measurement of BP and Microalbuminuria

After 5 min of seated rest each subject's BP was measured twice by a trained nurse using a sphygmomanometer and the average value was used for this analysis. Prehypertension was defined as SBP 120–139 mmHg or DBP 80–89 mmHg according to the 7th criteria of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure and the International Society of Hypertension. Prehypertension was subdivided into 2 groups based on the 2003 ESH-ESC guidelines for the management of arterial hypertension. Subjects with SBP between 120 and 129 mmHg or DBP between 80 and 84 mmHg were classified as the normal BP group. Subjects with SBP between 130 and 139 mmHg or DBP between 85 and 89 mmHg were classified as the high normal BP group.

A voided morning urine sample, at the baseline examination, was used to measure urinary albumin concentration as determined by radioimmunoassay (ICN, gamma counter micromedic 27027 USA). The urine albumin creatinine ratio (UACR) was used as the index of the urine albumin excretion. To define microalbuminuria in morning urine specimens, we used the UACR cutoff value of 30–300 μg/mg for both men and women. Subjects with UACR <30 μg/mg were defined as having normoalbuminuria, and those with UACR >300 μg/mg were defined as having macroalbuminuria.

Assessment of Metabolic Syndrome (MS)

MS was defined using the World Health Organization-West Pacific Region guidelines when 3 or more of the following conditions were present: (a) abdominal obesity (waist circumference >90 cm for men, >80 cm for women); (b) triglyceride (TG) concentration ≥1.70 mmol/L (150 mg/dl); (c) high-density lipoprotein (HDL)-cholesterol (C) <1.04 mmol/L (40 mg/dl) for men or <1.3 mmol/L (50 mg/dl) for women; (d) SBP/DBP ≥130/85 mmHg; and (e) fasting glucose ≥6.1 mmol/L (110 mg/dl).

Measurement of Other Variables

A blood sample was collected after more than 12h of fasting. Total cholesterol (TC) and TG were measured by enzymatic calorimetric testing. HDL-C and LDL-C were determined by the selective inhibition method and homogenous enzymatic calorimetric test using an automated analyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany), respectively. Serum insulin concentration was measured by the immunoradiometric method (Biosource, Belgium). The concentration of lipoprotein (a) (Lp(a)) was measured by the immunonephelometric assay (Behring Nephelometer II, Dade Behring, Marburg, Germany) using Latex Lp(a) reagent composed of polystyrene particles coated with rabbit anti-human Lp(a) IgG-globulin fraction. The minimum detectable Lp(a) level was 0.175 mg/L after 1:20 sample dilution.

Values are mean ± SD.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total (n=2,678)</th>
<th>High normal BP (n=739)</th>
<th>Normal BP (n=1,939)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.3 ± 11.0</td>
<td>51.5 ± 11.4</td>
<td>48.5 ± 10.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sex (male), n</td>
<td>1,692</td>
<td>492</td>
<td>1,200</td>
<td>0.015</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119.2 ± 8.0</td>
<td>127.4 ± 6.3</td>
<td>116.6 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.6 ± 4.4</td>
<td>81.9 ± 4.8</td>
<td>78.7 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (mm)</td>
<td>821 ± 85</td>
<td>835 ± 86</td>
<td>816 ± 85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.8</td>
<td>24.4 ± 2.9</td>
<td>23.8 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.1 ± 0.87</td>
<td>5.1 ± 0.87</td>
<td>5.1 ± 0.87</td>
<td>0.296</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.56 ± 0.06</td>
<td>1.69 ± 0.09</td>
<td>1.51 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.39 ± 0.31</td>
<td>1.36 ± 0.30</td>
<td>1.40 ± 0.31</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.97 ± 0.73</td>
<td>2.98 ± 0.74</td>
<td>2.97 ± 0.73</td>
<td>0.521</td>
</tr>
<tr>
<td>FBS (mmol/L)</td>
<td>5.35 ± 0.51</td>
<td>5.43 ± 0.52</td>
<td>5.3 ± 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>61.8 ± 24.3</td>
<td>62.5 ± 25.0</td>
<td>61.8 ± 23.6</td>
<td>0.447</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td>21.1 ± 17.5</td>
<td>20.3 ± 14.9</td>
<td>21.4 ± 14.8</td>
<td>0.123</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>91.3 ± 13.8</td>
<td>92.3 ± 14.0</td>
<td>91.0 ± 13.8</td>
<td>0.028</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0.32 ± 0.08</td>
<td>0.32 ± 0.09</td>
<td>0.31 ± 0.08</td>
<td>0.008</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>94.8 ± 80.7</td>
<td>102.6 ± 87.7</td>
<td>91.3 ± 77.0</td>
<td>0.005</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.12 ± 0.25</td>
<td>0.14 ± 0.30</td>
<td>0.11 ± 0.23</td>
<td>0.072</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.15 ± 0.92</td>
<td>2.20 ± 0.95</td>
<td>2.13 ± 0.91</td>
<td>0.088</td>
</tr>
<tr>
<td>UACR (μg/mg)</td>
<td>8.95 ± 21.97</td>
<td>11.06 ± 25.46</td>
<td>8.15 ± 20.43</td>
<td>0.006</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>3.4</td>
<td>4.9</td>
<td>2.8</td>
<td>0.009</td>
</tr>
<tr>
<td>MS (%)</td>
<td>9.8</td>
<td>25.1</td>
<td>4.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Insulin resistance (IR) was measured by homeostatic model assessment (HOMA)-IR and obtained by following formula:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (IU/ml)} \times \text{fasting blood glucose (mmol/L)}}{22.5}
\]

Statistical Analysis

The statistical analysis was conducted using SPSS version 12.0 software (Chicago, IL, USA). Continuous variable data are presented as the mean and standard deviation. Student’s t-test was used for comparison of mean values among continuous variables. For dichotomous variables, the \( \chi^2 \) test was used to evaluate a statistical difference among groups. Microalbuminuria was considered as a dependent variable and multivariate logistic regression analyses were used to test the independent relationships among microalbuminuria and several continuous or categorical parameters. A p-value <0.05 was considered statistically significant.

Results

Of the 2,678 prehypertensive subjects, the high-normal BP group was composed of 739 subjects (492 men, 247 women), and the normal BP group was composed of 1,939 subjects (1,197 men, 742 women). The baseline characteristics of the study population are given in Table 1.

Subjects with high normal BP were older, there were more males, and there were higher prevalences of larger waist circumference and body mass index, high levels of TG, fasting blood glucose, uric acid and ferritin, and lower levels of HDL-C than in those with normal BP.

The prevalence of MS in all subjects was 9.8% and it was more prevalent in subjects with high-normal BP was higher than in those with normal BP (25.1% vs 4%, p<0.001). The average value of the UACR in all subjects was 8.95±21.97 g/mg and microalbuminuria was identified in 91 subjects (3.4%).

The average value of UACR in subjects with high-normal BP was higher than in those with normal BP (11.06±25.46 g/mg vs 8.15±20.43 g/mg, p=0.006). In addition, the prevalence of microalbuminuria in subjects with high-normal BP was also higher than in those with normal BP (4.9% vs 2.8%, p=0.009) (Table 1).

Comparative analysis between microalbuminuric and normoalbuminuric subjects showed that microalbuminuric subjects had higher DBP, TC, fasting insulin, HOMA and a higher prevalence of MS than normoalbuminuric subjects (Table 2).

The univariate regression analyses showed that microalbuminuria was significantly associated with high normal BP category, fasting insulin, HOMA, TC, TG and the MS. However, microalbuminuria was not associated with age, sex, serum creatinine or HDL-C and was borderline associated with uric acid (Table 3).

The multiple logistic regression models including the above risk factors showed the high normal BP category had an independently significant association with microalbuminuria (OR=1.692, 95% confidence interval 1.097–
The high prevalence of microalbuminuria in subjects with high-normal BP was higher than in those with normal BP. In particular, our multivariate model showed that the high-normal BP category was significantly associated with an increased OR for the presence of microalbuminuria, as compared with the normal BP category.

Prehypertension is present in approximately 31% of the general adult population and has become a major public health concern. Two large epidemiological studies have reported data on individuals with high-normal BP. The Framingham study noted the clinical significance of prehypertension; the first prospective study of 9,745 subjects during 4 years of follow-up reported that subjects with high-normal BP had a markedly increased risk of developing sustained hypertension, compared with the optimal BP group, and the study emphasized the importance of weight control as a measure for primary prevention of hypertension.

A second study of an 11-year cohort of 6,859 subjects reported that high-normal BP was an independent predictor of cardiovascular complications (hazard ratio = 2.5 in women and 1.6 in men, when compared with subjects with optimal BP values).

By contrast, an analysis of a large cohort in the National Health and Nutrition Examination Survey (NHANES II) and NHANES II mortality study has reported that prehypertension was not independently associated with increased all-cause or cardiovascular disease mortality. However, a comparison of the mortality in the high-normal BP and normal BP groups was not done.

Microalbuminuria has been demonstrated as a marker for vascular dysfunction, including endothelial dysfunction. Microalbuminuria is associated with an increased risk of cardiovascular morbidity and mortality in patients with diabetes, hypertension, and in the general population. Urinary albumin excretion has been also reported as a predictor of developing hypertension and BP progression. The high prevalence of microalbuminuria in the high-normal BP group of the present subjects with apparent normal renal function may reflect increased glomerular filtration pressure in response to elevated BP. Another large recent study of 8,751 non-hypertensive subjects in the NHANES III cohort found that high-normal BP and normal BP categories were significantly associated with increased OR of microalbuminuria, compared with optimal BP (OR = 2.13; 1.34, respectively). Our results also demonstrated that the high-normal BP group had a higher prevalence of microalbuminuria than the normal BP group. However, unlike our study, the NHANES III cohort study did not include several other factors that influence microalbuminuria, such as serum creatinine, serum uric acid and the MS.

A prospective study of 1,499 non-diabetic, non-hypertensive individuals has demonstrated that those in the highest quartile of the UACR had an adjusted OR of 1.93 for developing hypertension and 1.45 for BP progression. Those data suggest that subclinical abnormalities in the kidney or vascular endothelium might precede the progression to higher BP.

In the present study, subjects with high-normal BP had higher risk profiles, as has been reported previously. Despite this, the BP status was independently associated with microalbuminuria, which suggests that we might need to consider dividing individuals into 2 groups for the management of prehypertension, especially for those with high-risk profiles.

Current guidelines have recommend that subjects with high-normal BP values be managed with lifestyle modifications! The Dietary Approaches to Stop Hypertension (DASH) dietary pattern, weight loss, reduced sodium intake, physical activity and moderation of alcohol intake) have been shown in clinical trials to prevent the development of hypertension.

Despite intensive community efforts to promote healthy lifestyles, however, the prevalence of prehypertension and hypertension continue to increase.

Recently, Julius et al reported that in a randomized prospective study including 809 participants in the high-normal BP category, the absolute reduction in the incidence of new-onset hypertension at 2 years with candesartan was 26.8%, as compared with 8% with lifestyle intervention. That result implies the need for additional studies to evaluate the clinical outcome of more active treatment in the high-normal BP group.

### Study Limitations

First, our study was a cross-sectional survey and could not determine cause-and-effect relationships. Second, our study subjects may not be fully representative of the general adult population, because they were enrolled in our study for the purpose of a general health examination. Third, the diagnosis of the high-normal and normal BP groups was based on the mean of 1 session. The JNC-7 classification requires the mean of BP readings from 2 or more office visits in order to prevent misclassification with the mean recording from 1 session. Forth, only 1 morning urine sample was collected for assessment of microalbuminuria. Thus, false-positive results may have occurred; the mean of the UACRs measured in multiple samples may provide more accurate results. However, we included a relatively large, community-based sample of middle-aged prehypertensive Korean individuals without diabetes, and describe

<table>
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<tr>
<th>Table 4 Multiple Logistic Regression Analyses for Prevalence of Microalbuminuria According to BP Category</th>
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<tbody>
<tr>
<td><strong>Standardized OR</strong></td>
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<td>----------------------</td>
</tr>
<tr>
<td>Univariate</td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>Model 2</td>
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<tr>
<td>Model 3</td>
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*Model 1 includes BP category and lipid profile.*
*Model 2 includes covariates of model 1, serum creatinine and uric acid.*
*Model 3 includes covariates of model 2 and HOMA.*

Abbreviations as in Tables 1, 3.
concrete differences in the conventional cardiovascular risk factors of the 2 BP categories.

In conclusion, subjects with high-normal BP have greater risk factors for cardiovascular disease, including microalbuminuria, than those with normal BP. Our study results suggest a more aggressive approach to treatment for individuals with high-normal BP for early prevention of cardiovascular disease. Elevated urinary albumin excretion may predict the development of hypertension. Moreover, microalbuminuria may be a surrogate marker for increased cardiovascular risk in individuals with high-normal BP. Therefore, further investigations are needed to ascertain whether alteration in microalbuminuria in this BP category might prevent or delay development of hypertension and cardiovascular events.

References