Microalbuminuria in 411 Untreated Individuals With Established Hypertension, White Coat Hypertension, and Normotension

Asbjørn Høegholm, Lia E. Bang, Kjeld S. Kristensen, Jakob W. Nielsen, Jan Holm

Abstract We compared urinary albumin excretion in normotensive subjects and patients with white coat and established hypertension. The study involved prospective comparison of office blood pressure, daytime ambulatory blood pressure, and urinary albumin excretion in consecutive patients (n=284) who were selected from general practice with newly diagnosed mild to moderate hypertension before the institution of pharmacologic antihypertensive therapy. All patients had a diastolic office blood pressure above 90 mm Hg; 173 had a consistently elevated diastolic blood pressure (established hypertension), and 111 had an average daytime ambulatory blood pressure below 90 mm Hg (white coat hypertension). A sample of 127 subjects drawn from the Danish national register served as a normotensive control group. The main outcome measure was the ratio of early morning urinary albumin to creatinine. This ratio differed significantly among the three groups, being (on a molar basis) 21±69×10⁻⁶ in the normotensive subjects, 22±39×10⁻⁶ in the white coat hypertensive patients, and 51±177×10⁻⁶ in patients with established hypertension. The difference remained significant after correction for covariables. The ratio of early morning urinary albumin to creatinine was weakly but significantly correlated to blood pressure, was more pronounced for ambulatory than for office measurements, was more pronounced for systolic than for diastolic pressure, and was more pronounced for hypertensive than for normotensive individuals. The ratio was as reproducible a measure as 24-hour albumin excretion. We conclude that white coat hypertensive patients have less renal involvement than patients with established hypertension but more than a normotensive control group. (Hypertension. 1994;24:101-105.)

Key Words • albuminuria • blood pressure, ambulatory • hypertension, essential • hypertension, white coat

The white coat phenomenon—ie, a pressor effect related to office examination compared with blood pressure measurement in a patient's usual surroundings—can, if sufficiently pronounced, cause misclassification of some normotensive individuals as hypertensive (white coat hypertension). Among patients with mild to moderate hypertension, the proportion of white coat hypertensive patients has been estimated to be between a quarter and a third. As data on the risk associated with a diagnosis of white coat hypertension are still not available, the condition cannot be claimed to be benign. Until prospective studies on morbidity and mortality are available, studies using surrogate end points must be our guide when deciding whether or not to treat these patients. Some studies indicate that white coat hypertensive patients have less cardiac involvement than patients with established hypertension, but studies evaluating the hypertensive effect on other end organs are still needed.

Increased urinary albumin excretion is found more frequently in hypertensive patients and proteinuria is associated with an excess morbidity and mortality. The aim of this study was to examine and compare the extent of microalbuminuria in normotensive subjects and in patients with white coat and established hypertension.

Methods

Patients

To estimate the frequency of white coat hypertension we performed 24-hour ambulatory blood pressure monitoring in 422 consecutive patients with newly diagnosed mild to moderate hypertension. The inclusion criteria were that their general practitioner had planned to start antihypertensive treatment but had not yet instituted it. Results from the first 159 patients showed that a quarter to a third of the patients could be classified as having white coat hypertension (daytime ambulatory diastolic blood pressure <90 mm Hg). To make the patients comparable with the normotensive subjects mentioned below, patients with known diabetes or renal disease were excluded from the statistical analyses.

As part of a multicenter study to establish the distribution of ambulatory blood pressure in the population, we performed 24-hour blood pressure monitoring in subjects drawn at random from the Danish national register. Subjects with known renal disease, diabetes, hypertension, or other conditions necessitating therapy with drugs with antihypertensive effects were excluded, leaving 146 subjects.

The study was in accordance with The Second Declaration of Helsinki and was approved by the local ethics committee. All participating subjects gave their informed consent.

Blood Pressure Measurements

All referred patients were considered by their general practitioner to have hypertension and were scheduled to start antihypertensive treatment in the near future. No patient had...
for the last month before the study received any antihypertensive drug; however, a third had previously been on such medication, in most cases because of hypertension, which had been treated for a median of 3 years. The blood pressure of patients who had never been on antihypertensive medication had been followed by the general practitioner for a median of 4 months. The practitioners reported that they had determined the blood pressure at least three times (median, four) with at least weekly intervals. Nearly everybody used a standard-sized cuff (12x35 cm) with patients seated; approximately a third used aneroid sphygmomanometers, and the remainder used mercury columns. The average diastolic blood pressure was above 90 mm Hg in all subjects.

Office blood pressure of the normotensive subjects was determined as the mean of five measurements with a Hawksley random-zero sphygmomanometer, performed with subjects in the sitting position after 15 minutes of rest in the hypertension clinic.

The subjects wore TM 2420 ambulatory blood pressure recorders (A&D) for at least 24 successive hours on working days, during which period they went about their normal daily activities. The recorders took readings every 15 minutes during the day (7 AM to 10:59 PM) and every 30 minutes during the night (11 PM to 6:59 AM). In each individual the recordings were adjusted by a calibration factor obtained by five simultaneous Hawksley readings on the opposite arm. The influence of different sampling intervals and missing values was minimized by computing hourly averages and subsequently using these figures for the determination of the average daytime ambulatory blood pressure, the average nighttime ambulatory blood pressure, and the average 24-hour ambulatory blood pressure. An average daytime ambulatory blood pressure above 90 mm Hg was considered hypertensive; this level corresponds fairly to the 95th percentile of the normotensive population. All subjects yielded acceptable ambulatory readings, defined as at least 18 daytime readings from outside the office.

Urinalysis
All subjects were asked to bring with them an early morning urine sample (EMU), defined as the first voided specimen on arising. Albuminuria was estimated as both albumin concentration and albumin-creatinine ratio. For evaluation of the reproducibility of the albumin excretion measures, a subsample of 22 of the normotensive subjects was prompted to deliver two 24-hour urine collections with separate EMUs; the collections were performed on working days fewer than 7 days apart. In the 24-hour samples, albumin concentration, total amount of albumin (albumin excretion rate), and albumin-creatinine ratio were determined.

Urine samples were stored at −20°C until analyses were carried out using the same batches of reagents. Albumin concentrations were determined by an immunonephelometric technique. Creatinine concentrations were measured by the routine Jaffé method (SMA-II, Technicon).

Statistical Analyses
Data are expressed as mean±SD unless otherwise stated; as the microalbuminuria data were skewed, they were transformed logarithmically before being statistically tested. A χ² test was used for group comparisons regarding categorized data. Group comparisons regarding continuous variables were performed with one-way ANOVA followed by the Student-Newman-Keuls procedure. A value of P<.05 was considered significant. The main outcome measure was furthermore checked by entering control variables into an analysis of covariance (ANCOVA). Univariate correlation was analyzed by standard statistical methods. A stepwise multiple regression analysis with inclusion at the .01 level and exclusion at the .05 level was used to evaluate the influence of gender, age, weight, height, body mass index (BMI), pulse, and practitioner’s and ambulatory blood pressures on microalbuminuria; these last criteria were applied in order to limit the number of statistically significant blood pressure parameters. All computations were carried out with SPSS/PC+ software (SPSS).

Results
Three hundred and two hypertensive patients (71.6% of the eligible patients) delivered an EMU, but 18 were excluded because of diabetes and/or renal disease, leaving 284 for statistical analyses. When evaluated by ambulatory monitoring, 173 were hypertensive (diastolic daytime ambulatory blood pressure >90 mm Hg), and 111 were white coat hypertensives (diastolic daytime ambulatory blood pressure ≤90 mm Hg). One hundred twenty-seven normotensive subjects (87.0% of eligible) were also included in the study. Table 1 gives demographic data, blood pressures, and pulse values for the three groups. The groups were comparable regarding demographic data except age; this difference was due to the normotensive subjects being intentionally recruited with an even distribution. There were highly significant differences in all data on blood pressure and pulse; the Student-Newman-Keuls procedure showed that the hypertensive group differed significantly from the other groups in all variables, whereas the white coat group differed from the normotensive group with regard to systolic and diastolic office blood pressures, nighttime diastolic blood pressure, and nighttime pulse.

In neither the hypertensive patients nor the normotensive control subjects did the eligible subjects differ statistically significantly from the ineligible subjects with regard to the characteristics given in Table 1. Table 2 gives the results of the reproducibility testing of the different methods of quantifying microalbuminuria. No statistically significant differences were found between the methods of measurement.

Table 3 shows the main results of the study, ie, the microalbuminuria in EMU of the three patient groups. After logarithmic transformation, both urinary albumin concentration and the albumin-creatinine ratio were significantly different among the three groups. The Student-Newman-Keuls procedure showed that there were differences among all three groups for both measures. When age, gender, BMI, height, weight, and office blood pressure were entered as control variables in an ANCOVA, the difference in albumin excretion remained statistically significant.

The 95th percentile of albumin excretion in the normotensive group was 50.6×10⁻⁶ (albumin-creatinine ratio on a molar basis) or 0.50 mmol/L. Six normotensive subjects (5%) had values above this level, whereas among the white coat hypertensive patients there were 12 (10.2%) and 14 (11.9%), respectively, and among the established hypertensive patients, 26 (14.1%) and 27 (14.7%), respectively. These differences were statistically significant.

Table 4 shows the univariate correlations between microalbuminuria data and blood pressures for the normotensive subjects and hypertensive patients. Correlations tend to be better for the log of the ratio between albumin and creatinine and for systolic blood pressures, but all correlations are weak, ie, below .30. There were no significant correlations between gender or pulse and microalbuminuria. In the multiple regression analysis, the logarithm of albumin concentration
TABLE 1. Blood Pressures and Demographic Data for Normotensive Subjects and Patients With White Coat or Established Hypertension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normotensive (n=127)</th>
<th>White Coat Hypertensive (n=111)</th>
<th>Established Hypertensive (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.4±15.4</td>
<td>46.6±12.6</td>
<td>47.8±12.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.0±13.6</td>
<td>74.0±14.3</td>
<td>74.3±16.0</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71±0.09</td>
<td>1.71±0.10</td>
<td>1.70±0.09</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.0±3.7</td>
<td>25.2±3.6</td>
<td>25.7±4.5</td>
</tr>
<tr>
<td>Office BP, mm Hg</td>
<td>130.5±19.0/82.3±11.3</td>
<td>161.2±16.4/100.7±6.3</td>
<td>160.5±18.9/105.3±7.7</td>
</tr>
<tr>
<td>Average daytime ambulatory BP, mm Hg</td>
<td>129.5±18.9/82.6±11.0</td>
<td>132.9±14.6/84.0±5.1</td>
<td>150.2±16.1/101.4±7.5</td>
</tr>
<tr>
<td>Average nighttime ambulatory BP, mm Hg</td>
<td>111.6±20.8/70.5±11.1</td>
<td>116.1±16.7/73.3±7.0</td>
<td>129.7±21.0/87.6±11.0</td>
</tr>
<tr>
<td>Average 24-hour ambulatory BP, mm Hg</td>
<td>123.2±19.0/78.4±10.8</td>
<td>127.4±14.3/80.4±5.0</td>
<td>143.4±16.8/96.8±7.9</td>
</tr>
<tr>
<td>Daytime pulse, min⁻¹</td>
<td>75.5±8.1</td>
<td>77.1±9.1</td>
<td>79.9±8.5</td>
</tr>
<tr>
<td>Nighttime pulse, min⁻¹</td>
<td>63.3±8.3</td>
<td>66.2±10.2</td>
<td>68.9±9.1</td>
</tr>
<tr>
<td>24-Hour pulse, min⁻¹</td>
<td>71.2±7.9</td>
<td>72.8±9.1</td>
<td>76.3±8.1</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. White coat hypertension was defined as an average daytime diastolic blood pressure ≤90 mm Hg; established hypertension as average daytime diastolic blood pressure >90 mm Hg. Data except gender are expressed as mean±SD. P values refer to difference between the three groups. Comparison for gender was made by χ² test, for other data by one-way ANOVA.

was associated with systolic ambulatory daytime blood pressure, age, and systolic office blood pressure (R²=.106), whereas the logarithm of the ratio between albumin and creatinine concentrations was associated with systolic ambulatory daytime and systolic office blood pressures (R²=.156). BMI, gender, pulse, and nighttime or diastolic blood pressures did not add information in this statistical model.

Discussion

Office blood pressure measurements have traditionally been the basis for diagnosing and monitoring arterial hypertension. With the introduction of ambulatory blood pressure measurements, a new subgroup of the hypertensive population has emerged, namely, white coat hypertensive patients. The natural history of these patients is largely unknown. Until prospective studies using morbidity and mortality as end points are completed, the decision whether to treat them as hypertensive (based on indirect evidence) or normotensive subjects, that the coefficient of variation in 22 normotensive subjects has to be based on indirect evidence. It could be argued that most reliance can be put on the ambulatory measurements, because these measurements are more strongly associated with end-organ damage,14,15 with mortality,16 and with morbidity and mortality. According to this view, the white coat patients should not be treated as hypertensive. Studies examining the cardiac geometry of white coat hypertensive patients give some support to this view: white coat hypertensive patients definitely display less cardiac involvement than do patients with established hypertension.43 The answer must depend more on comparison with normotensive subjects, but in one of the cited studies4 normotensive control subjects were missing; the other study4 showed, despite a relatively small number of subjects, that the white coat hypertensive patients had a significantly thicker posterior wall.

Estimating albumin excretion in hypertensive patients is probably nearly as valuable a surrogate end point as is cardiac geometry. Albuminuria is a predictor of cardiovascular morbidity4,17 and mortality.7,17,18 Low-level albuminuria, so-called microalbuminuria, is present more often and to a larger extent in hypertension than in normotension,6,7,19,20 and it tends to decrease during antihypertensive treatment.31,22 The hypertensive albuminuria is glomerular6 and varies with posture and exercise.23

The gold standard for determination of urinary albumin excretion has long been the collection of urine throughout a 24-hour period,24 but there is good evidence indicating that shorter collection periods24 or even single voided samples25 are applicable, especially if collected during the night or as an EMU to avoid the influence of posture and exercise.26 Some authors25,26 recommend that the albumin concentration in the urine should be related to the creatinine concentration, but the issue seems not to be crucial.24,26 We found in a subgroup of our normotensive subjects that the coeffi-
Table 3. Albumin Excretion in Normotensive Subjects and Patients With White Coat and Established Hypertension

<table>
<thead>
<tr>
<th>Measure of Albuminuria</th>
<th>Normotensive (n=127)</th>
<th>White Coat Hypertensive (n=111)</th>
<th>Established Hypertensive (n=173)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary albumin concentration, µmol/L</td>
<td>0.21±0.70</td>
<td>0.24±0.41</td>
<td>0.38±0.81</td>
<td>.085</td>
</tr>
<tr>
<td>Log U-albumin</td>
<td>0.83±0.40</td>
<td>0.96±0.42</td>
<td>1.09±0.44</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urinary creatinine concentration, mmol/L</td>
<td>11.0±5.2</td>
<td>11.8±6.3</td>
<td>11.3±5.7</td>
<td>.549</td>
</tr>
<tr>
<td>Urinary albumin-creatinine ratio, ×10^{-6}</td>
<td>20.9±69.4</td>
<td>22.0±38.6</td>
<td>51.2±177</td>
<td>.054</td>
</tr>
<tr>
<td>Log U-albumin-creatinine ratio</td>
<td>-0.16±0.36</td>
<td>-0.05±0.36</td>
<td>0.10±0.45</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Log U-albumin indicates the logarithmic transformed urinary albumin concentration. Data are expressed as mean±SD. P values refer to statistical testing by one-way ANOVA.

cients of variation for repeated measures were similar regardless of whether urine was collected over 24 hours or was an EMU (Table 2). Furthermore, the figures are comparable to those reported by other researchers using 24-hour collections. This indicates that urinary albumin excretion can be determined as reliable with measurements based on EMU as with measurements obtained by 24-hour urine collections. The 95th percentiles for urinary albumin-creatinine ratio and albumin concentration in the normotensive subjects in the present study were 50.6×10^{-6} and 0.50 mmol/L, which are similar to the figures reported by others.

In the present study, we found that the white coat hypertensive patients had a lower albumin excretion than the patients with established hypertension, but it was higher than that of the normotensive control subjects. The significance of the difference remained after all other data available before the ambulatory monitorings were entered.

Albumin excretion correlated significantly with blood pressure in both the normotensive and hypertensive population, but all the correlations were weak (Table 4). In general, the correlations were better for systolic than diastolic blood pressures, for ambulatory than office blood pressures, and for hypertensive than normotensive individuals, but the differences are subtle. However, it must be borne in mind that we studied newly diagnosed hypertensive patients, in whom the effect of the raised blood pressure on the kidneys had been relatively short. The trend for stronger correlations for systolic blood pressures is interesting, because the same trend is found when cardiac geometry is examined and because treatment of isolated systolic hypertension is shown to be clearly beneficial. Somewhat unexpectedly, the association between albumin excretion and nighttime blood pressure (the period of urine production in our study) was in no way stronger than for the daytime blood pressure. Others studies have reported a similar tendency for stronger correlations in hypertensive than normotensive individuals and in ambulatory pressures compared with casual, whereas diastolic pressures have been reported superior to systolic pressures, in contrast with our findings. Some studies have found no statistically significant correlations between blood pressure and albuminuria. A study on obesity has shown a possible correlation between BMI and albuminuria; our study gives some support for this finding, but only in the normotensive subjects.

In conclusion, we have found that albumin excretion can be reliably determined in EMU, that it correlates with blood pressure, and that white coat hypertensive patients in this regard display less target-organ involvement than do patients with established hypertension. However, the white coat patients had a slightly though statistically significantly higher albumin excretion than did the normotensive subjects, indicating that they may.

Table 4. Univariate Correlates of Albumin Excretion in Normotensive Subjects (n=127) and Hypertensive Patients (n=284)

<table>
<thead>
<tr>
<th></th>
<th>Albumin Concentration</th>
<th>Log U-Albumin Concentration</th>
<th>Albumin-Creatinine Ratio</th>
<th>Log U-Albumin-Creatinine Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.07/0.04</td>
<td>0.01/0.07</td>
<td>0.12/0.14*</td>
<td>0.30/0.11</td>
</tr>
<tr>
<td>Weight</td>
<td>0.20/0.01</td>
<td>0.21*/0.09</td>
<td>0.19/0.09</td>
<td>0.10/0.13</td>
</tr>
<tr>
<td>Height</td>
<td>0.04/0.01</td>
<td>0.07/0.04</td>
<td>0.03/0.06</td>
<td>-0.09/0.14*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.22*/0.03</td>
<td>0.20/0.01</td>
<td>0.22*/0.09</td>
<td>0.18/0.09</td>
</tr>
<tr>
<td>Systolic office BP</td>
<td>0.20/0.10</td>
<td>0.19/0.06</td>
<td>0.23*/0.11</td>
<td>0.341/0.18*</td>
</tr>
<tr>
<td>Diastolic office BP</td>
<td>0.24*/0.02</td>
<td>0.20/0.02</td>
<td>0.26*/0.05</td>
<td>0.30/0.03</td>
</tr>
<tr>
<td>Systolic daytime ambulatory BP</td>
<td>0.18/0.21†</td>
<td>0.21*/0.21†</td>
<td>0.20/0.21†</td>
<td>0.30/0.30†</td>
</tr>
<tr>
<td>Diastolic daytime ambulatory BP</td>
<td>0.14/0.11</td>
<td>0.12/0.17*</td>
<td>0.15/0.09</td>
<td>0.17/0.19*</td>
</tr>
<tr>
<td>Systolic nighttime ambulatory BP</td>
<td>0.18/0.20†</td>
<td>0.16/0.21†</td>
<td>0.19/0.28†</td>
<td>0.26*/0.32†</td>
</tr>
<tr>
<td>Diastolic nighttime ambulatory BP</td>
<td>0.22*/0.14*</td>
<td>0.12/0.18*</td>
<td>0.22*/0.19*</td>
<td>0.170/0.23†</td>
</tr>
</tbody>
</table>

Log U-albumin indicates the logarithmic transformed urinary albumin concentration; BP, blood pressure. Values are normotensive/hypertensive.

*P<.01, †P<.001.
be a group at intermediate risk. We suggest that the decision whether or not to treat these patients pharmacologically should depend on the presence of target-organ damage or other risk factors (such as smoking, dyslipidemia, and familial history).

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References


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