Arterial Hypertension, Microalbuminuria, and Risk of Ischemic Heart Disease

Jan Skov Jensen, Bo Feldt-Rasmussen, Svend Strandgaard, Marianne Schroll, Knut Borch-Johnsen

Abstract—Albumin excretion in urine is positively correlated with the presence of ischemic heart disease and atherosclerotic risk factors. We studied prospectively whether a slight increase of urinary albumin excretion, ie, microalbuminuria, adds to the increased risk of ischemic heart disease among hypertensive subjects. In 1983 and 1984, blood pressure, urinary albumin/creatinine concentration ratio, plasma total and HDL cholesterol levels, body mass index, and smoking status were obtained in a population-based sample of 2085 subjects, aged 30 to 60 years, who were free from ischemic heart disease, diabetes mellitus, and renal or urinary tract disease. Untreated arterial hypertension or borderline hypertension was present in 204 subjects, who were followed until 1993 by the National Hospital and Death Certificate Registers with respect to development of ischemic heart disease. During 1978 person-years, 18 (9%) of the hypertensive subjects developed ischemic heart disease. Microalbuminuria, defined as a urinary albumin/creatinine ratio above the upper decile (1.07 mg/mmol), was the strongest predictor of ischemic heart disease, with an unadjusted relative risk of 4.2 (95% CI 1.5 to 11.9, \( P = 0.006 \)) and a relative risk of 3.5 (95% CI 1.0 to 12.1, \( P = 0.05 \)) when adjusted for all other atherosclerotic risk factors, including age and gender. In conclusion, microalbuminuria confers a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects. Urinary albumin excretion should be measured regularly in a hypertension clinic, and a rigorous control of blood pressure and of other atherosclerotic risk factors is recommended in hypertensive patients with microalbuminuria. (Hypertension. 2000;35:898-903.)

Key Words: atherosclerosis ■ hypertension, arterial ■ ischemia ■ microalbuminuria ■ heart

Arterial hypertension is, in some patients, associated with a subclinical increase of the albumin excretion in the urine, ie, microalbuminuria, in spite of preserved renal function.\(^1\)\(^2\) In hypertensive subjects, microalbuminuria has often been related to an excess of atherosclerotic cardiovascular disease,\(^2\)\(^3\) which is more frequent in the hypertensive population,\(^4\) and to an increased level of atherosclerotic risk markers.\(^5\)\(^6\)\(^7\) In populations of diabetic patients as well as in the general population, microalbuminuria independently precedes atherosclerotic cardiovascular disease,\(^8\)\(^9\)\(^10\)\(^11\)\(^12\) but this has never been established among hypertensive subjects.

In the present study, we describe a 10-year follow-up analysis of all subjects with untreated arterial hypertension or borderline hypertension identified within the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study in Denmark, 1983 and 1984.\(^13\)\(^14\) Arterial hypertension was defined according to the WHO criteria. The definition of microalbuminuria has been used in previous studies by our group\(^15\)\(^-\)\(^22\) and follows a recommendation by Mogensen,\(^23\) ie, a urinary albumin excretion above the upper decile in the entire population under study. The aim of the analysis was to assess the predictive impact of microalbuminuria on the subsequent development of ischemic heart disease among young and middle-aged individuals with arterial hypertension or borderline hypertension.

Methods

Subjects and Study Design

Between 1983 and 1984, blood pressure, urinary albumin excretion, and other atherosclerotic risk factors were measured in 2085 subjects born in 1922, 1932, 1942, or 1952. The ascertainment was 74%. Individuals were excluded from this analysis if they, at baseline, had ischemic heart disease (International Classification of Diseases, 8th revision [ICD-8] code No. 410-414),\(^24\) diabetes mellitus, renal or urinary tract disease, an abnormal ultrasonic examination of the kidneys or urinary tract, or dipstick-positive glucosuria or hematuria. The participants gave informed consent, and the study was in accordance with the Declaration of Helsinki.

With patients in the sitting position, systolic and diastolic blood pressures were measured 3 times within a 30-minute period with a London School of Hygiene sphygmomanometer and an appropriately sized cuff. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V). Arterial hypertension or borderline hypertension, defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg, was observed in 204 participants not treated with antihypertensive medication.
Urinary albumin excretion was expressed as the albumin/creatinine concentration ratio in an early morning spot urine sample. The albumin concentration was measured by an ELISA (lower detection limit, 0.1 mg/L; intra-assay variation, 2.1%; and interassay variation, 8.3%). and the creatinine concentration was measured by a colorimetric method (intra-assay variation, 1.0%; interassay variation, 2.0%) after 12 to 13 years of frozen storage. Microalbuminuria was defined as a urinary albumin/creatinine ratio >1.07 mg/mmol (the upper decile in the entire study population of 204 hypertensives, 1.05 mg/mmol in men and 1.08 mg/mmol in women); normoalbuminuria was defined as a urinary albumin/creatinine ratio ≤1.07 mg/mmol.

A fasting blood sample was drawn for the measurement of plasma total cholesterol and HDL cholesterol (enzymatic colorimetric methods [CHOL CHOD-PAP and HDL CHOLESTEROL PRECIPITANT], Peridochrom, Boehringer-Mannheim GmbH). Body mass index was calculated as weight/height², and smoking status was recorded.

On the basis of the Danish personal identification code, the 204 hypertensive individuals were followed until death, emigration, or December 31, 1993. Information regarding vital status, cause of death, hospital admissions, and diagnosis were traced by use of the National Register on Vital Status, the National Death Certificate Register, and the National Hospital Discharge Register, respectively. We identified 18 cases with fatal or nonfatal myocardial infarction, angina pectoris, or ischemic heart disease (ICD-8 code No. 410-414).

Statistical Analysis

Differences in baseline characteristics between hypertensives developing ischemic heart disease and hypertensive controls were compared by the Student unpaired t test for continuous variables and by the χ² test with the Yates continuity correction for categorical variables. The effects of the baseline variables on the risk of developing ischemic heart disease were analyzed by Cox proportional hazards regression analysis. The final model for the optimal prediction of ischemic heart disease was fitted by backward elimination of insignificant baseline variables (P≥0.05).

Survival free from ischemic heart disease during the follow-up period was compared between microalbuminuric and normoalbuminuric hypertensives by a Kaplan-Meyer plot with use of log-rank test statistics. A value of P<0.05 was considered to be of statistical significance.

The statistical analyses were run on the software package SPSS for Windows.

Results

During 1978 person-years of follow-up, 18 of the 204 hypertensive subjects (9%) developed ischemic heart disease. At baseline, microalbuminuria was present in 28% (95% CI 7 to 49) of those who subsequently developed ischemic heart disease compared with only 8% (95% CI 4 to 12) of the controls (P=0.02, Table 1). Four of the cases were women with urinary albumin/creatinine ratios of 8.36, 1.08, 1.06, and 0.89 mg/mmol. Hypertensives who developed ischemic heart disease were furthermore characterized by higher systolic blood pressure (153 [95% CI 148 to 158] mm Hg versus 148 [95% CI 147 to 149] mm Hg, P=0.05) and plasma total cholesterol concentration (7.2 [95% CI 6.6 to 7.8] mmol/L versus 6.5 [95% CI 6.3 to 6.7] mmol/L, P=0.03) than those who remained free from ischemic heart disease (Table 1).

Table 2 shows the predictive impact of the baseline variables on the development of ischemic heart disease. Microalbuminuria, urinary albumin/creatinine ratio, plasma total cholesterol, and systolic blood pressure were all significantly and positively associated with the development of ischemic heart disease, whereas smoking failed, by a small margin, to obtain statistical significance. When adjusted for the effects of age, gender, total and HDL cholesterol, body mass index, and blood pressures, the relative risk of microalbuminuria for development of ischemic heart disease increased, whereas adjustment for the effect of smoking led to a slight decrease of the relative risk (Table 3). Survival free from ischemic heart disease in microalbuminuric and normoalbuminuric hypertensives is illustrated by a Kaplan-Meyer plot (Figure).
Table 4 shows the best model for prediction of ischemic heart disease among hypertensives. When microalbuminuria, male gender, and plasma total cholesterol were included in the model, none of the other baseline variables measured in the present study contributed to any significant further increase in the relative risk.

**Discussion**

This population-based prospective study of 204 subjects with untreated arterial hypertension or borderline hypertension has shown that the occurrence of microalbuminuria confers an increased risk of subsequent ischemic heart disease in hypertensives that is \( \times 4 \) times that in hypertensives or borderline hypertensives with normoalbuminuria, irrespective of the later use of antihypertensive therapy. Furthermore, the predictive effect of microalbuminuria seems to be independent of and stronger than the effect of the conventional atherosclerotic risk factors, such as smoking, dyslipidemia, obesity, high blood pressure, male gender, and advanced age.

Microalbuminuria was initially introduced as a predictor of impaired renal function among diabetic patients\(^{28,29}\) and was defined as a urinary albumin excretion of 30 to 300 mg over a 24-hour period.\(^{30}\) A later follow-up study of diabetics from our group has, in addition, suggested an increased risk of cardiovascular disease at even lower levels of urinary albumin excretion.\(^{10}\) Among subjects without diabetes mellitus, the urinary albumin excretion rarely exceeds 30 mg over a 24-hour period irrespective of present arterial hypertension.\(^{15,31}\) Within the Danish MONICA study, we recently observed an increased risk of ischemic heart disease confined to the 10% of the general population having the highest urinary albumin excretion.\(^{12}\) In accordance with this and a recommendation by Mogensen,\(^{23}\) we decided to define microalbuminuria as a urinary albumin excretion above the upper decile in the hypertensive population under study. To increase the compliance, we collected spot urine specimens and measured the albumin/creatinine concentration ratio, which is a precise index of urinary albumin excretion.\(^{25}\)

This is the first prospective population-based study of hypertensives that reports an independent predictive effect of microalbuminuria in the development of ischemic heart disease. Among hypertensive subjects screened within another Danish population study, the Copenhagen City Heart Study, we have described a cross-sectional relation between urinary albumin excretion and ischemic heart disease,\(^{3}\) thus confirming a previous report by Agrawal et al.\(^{2}\) Bigazzi et al.\(^{32}\) analyzed data obtained from a retrospectively selected hospital population of 141 hyperten-

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Relative Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men vs women</td>
<td>2.5 (0.6–10.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age in 10-y increments</td>
<td>1.04 (0.98–1.12)</td>
<td>0.14</td>
</tr>
<tr>
<td>Systolic blood pressure in 10 mm Hg increments</td>
<td>1.5 (1.0–2.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic blood pressure in 10 mm Hg increments</td>
<td>1.3 (0.8–2.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index in 1-kg/m(^2) increments</td>
<td>1.00 (0.90–1.11)</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoker vs nonsmoker</td>
<td>2.7 (1.0–7.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Plasma total cholesterol in 1-mmol/L increments</td>
<td>1.4 (1.1–1.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasma HDL cholesterol in 1-mmol/L increments</td>
<td>0.7 (0.3–2.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Urinary albumin/creatinine ratio in 1-mg/mmol increments</td>
<td>1.10 (1.02–1.18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Microalbuminuria vs normoalbuminuria</td>
<td>4.2 (1.5–11.9)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.

Table 3. Relative Risks With 95% CIs for Development of Ischemic Heart Disease Associated With Microalbuminuria Successively Adjusted for Other Baseline Characteristics in 204 Hypertensive Subjects

<table>
<thead>
<tr>
<th>Included Variables</th>
<th>Relative Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>4.2 (1.5–11.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Microalbuminuria, sex</td>
<td>4.5 (1.6–12.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Microalbuminuria, sex, lipoproteins</td>
<td>5.6 (1.9–16.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Microalbuminuria, sex, lipoproteins, body mass index</td>
<td>5.6 (1.9–16.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Microalbuminuria, sex, lipoproteins, body mass index, blood pressures</td>
<td>5.1 (1.6–16.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Microalbuminuria, sex, lipoproteins, body mass index, blood pressures, age</td>
<td>4.5 (1.4–14.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Microalbuminuria, sex, lipoproteins, body mass index, blood pressures, age, smoking</td>
<td>3.5 (1.0–12.1)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.
microalbuminuria may reflect an endothelial dysfunction and perhaps an augmented atherogenic susceptibility to other risk factors, including arterial hypertension. Solving this problem would require a longitudinal cohort study with repeated measurements of urinary albumin excretion and severity of atherosclerosis, eg, ultrasonic assessments of the intima-media thickness and flow-mediated vasodilation of arteries.37,38

Previous studies have demonstrated that microalbuminuria reflects a renal and systemic transvascular albumin leakage39–42 that is perhaps due to the low vessel wall content of heparan sulfate.43–46 In animal models, it has been shown that the transvascular leakage of albumin and lipoproteins are tightly correlated47,48 and that both are elevated in atherosclerosis49 and in atherosclerosis-prone sites of arteries.50

Study Limitations
It is a drawback of the present study that the hypertensive population followed was rather small in size. However, the population-based design and the high relative risk associated with microalbuminuria allow valid conclusions to be drawn. However, it cannot be completely excluded that the results observed are explained by selection bias, eg, bias due to low urinary albumin/creatinine ratio in nonresponders (26%) who may be physically inactive51 and thereby “at risk” for future ischemic heart disease.52 Furthermore, because a glucose tolerance test was not performed, a minor proportion of the population could have undiagnosed diabetes mellitus, thereby confounding the association between urinary albumin excretion and ischemic heart disease. The lack of knowledge about medication that was instituted during follow-up is also a limitation. It is well known that there is a considerable intrapersonal variation of urinary albumin excretion even in early morning spot urine samples.53 Because of regression dilution, this may have caused an underestimation of the existing positive association between urinary albumin excretion and the development of ischemic heart disease. Moreover, because albumin concentration in urine slightly declines during protracted frozen storage,54 the “at risk” level of urinary albumin/creatinine ratio (>1.07 mg/mmol) may have been underestimated, unless creatinine concentration declines similarly.

Conclusions
We conclude that microalbuminuria, defined as a urinary albumin excretion in the upper 10% range, is the strongest independent determinant of ischemic heart disease among subjects with arterial hypertension. On this basis, urinary albumin excretion should be measured regularly in hypertension clinic. Although intervention studies of the effect of lowering urinary albumin excretion on cardiovascular morbidity are missing, we recommend a rigorous control of blood pressure and other modifiable atherosclerotic risk factors in microalbuminuric hypertensives.

Acknowledgments
The study was supported by the Danish Medical Research Council (grant No. J12-2008-1), the Danish Heart Foundation, and the Danish Hypertension Society.
References


Arterial Hypertension, Microalbuminuria, and Risk of Ischemic Heart Disease
Jan Skov Jensen, Bo Feldt-Rasmussen, Svend Strandgaard, Marianne Schroll and Knut Borch-Johnsen

Hypertension. 2000;35:898-903
doi: 10.1161/01.HYP.35.4.898

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/35/4/898

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/