Very Low Levels of Microalbuminuria Are Associated With Increased Risk of Coronary Heart Disease and Death Independently of Renal Function, Hypertension, and Diabetes

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Background—The aim of this study was to assess the level of urinary albumin excretion (microalbuminuria), which is associated with increased risk of coronary heart disease and death, in the population. Microalbuminuria has been suggested as an atherosclerotic risk factor. However, the lower cutoff level of urinary albumin excretion is unknown. It is also unknown whether impaired renal function confounds the association.

Methods and Results—In the Third Copenhagen City Heart Study in 1992 to 1994, 2762 men and women 30 to 70 years of age underwent a detailed cardiovascular investigation program, including a timed overnight urine sample. The participants were then followed up prospectively by registers until 1999 with respect to coronary heart disease and until 2001 with respect to death. During follow-up, 109 incident cases of coronary heart disease and 276 deaths were traced. A urinary albumin excretion above the upper quartile, ie, 4.8 µg/min, was associated with increased risk of coronary heart disease (RR, 2.0; 95% CI, 1.4 to 3.0; *P*<0.001) and death (RR, 1.9; 95% CI, 1.5 to 2.4; *P*<0.001) independently of age, sex, renal creatinine clearance, diabetes mellitus, hypertension, and plasma lipids. Lower levels of urinary albumin excretion were not associated with increased risk.

Conclusions—Microalbuminuria, defined as urinary albumin excretion >4.8 µg/min (corresponding to ≈6.4 µg/min during daytime), is a strong and independent determinant of coronary heart disease and death. Our suggestion is to redefine microalbuminuria accordingly and perform intervention studies. (Circulation. 2004;110:32-35.)

Key Words: albumins [•] coronary disease [•] mortality [•] renal function

Microalbuminuria was originally defined among patients with diabetes mellitus as 20 to 200 µg albumin excreted in the urine per minute (15 to 150 µg/min in urine samples collected at night) and was associated with increased risk of chronic renal failure. Later, it was shown that microalbuminuria among patients with diabetes reflects systemic vascular damage and increased risk of coronary heart disease (CHD) independently of renal function. Microalbuminuria is present in 30% of middle-aged patients with either type 1 or type 2 diabetes mellitus. However, in persons without diabetes, urinary albumin excretion is generally far from the level seen in diabetes. Nevertheless, population studies of nondiabetic individuals have demonstrated that even small amounts of albumin excreted in the urine are associated with increased risk of CHD.

In the present study, we aimed to assess the lower cutoff level for urinary albumin excretion associated with increased risk of CHD and death. Furthermore, we measured renal function because it could affect the association between microalbuminuria and the risk of CHD and death.25

Methods

Study Population

The study was performed as a substudy of the Third Copenhagen City Heart Study, 1992 to 1994, a longitudinal epidemiological survey of cardiovascular disease and its known and potential risk factors. About 16,000 subjects were randomly drawn by the Copenhagen Population Register, and 10,200 (64%) participated. All participants between 30 and 70 years of age were asked to collect a timed overnight urine sample. A total of 3,645 urine samples were received. Included in the analysis were 2,762 participants (1,268 men, 1,494 women) who had no history of CHD for whom a total set of data were obtained. All subjects included gave their informed consent to participate. The study, performed in accordance with the Second Helsinki Declaration, was approved by the regional ethics committee.

Baseline Variables

Data about medication and smoking were recorded. Diabetes was defined as self-reported disease, use of antidiabetic medicine or insulin, and/or nonfasting plasma glucose ≥11.1 mmol/L (colorimetric enzymatic method). Blood pressure was measured in subjects in the sitting position on the left upper arm after a 5-minute rest. A London School of Hygiene sphygmomanometer was used. Hypertension was defined as systolic blood pressure >140 mm Hg.
diastolic blood pressure > 85 mm Hg, and/or use of antihypertensive drugs. Body mass index was calculated as weight divided by height squared. Plasma total and HDL cholesterol and serum creatinine were measured by enzymatic colorimetric methods.

The urinary albumin concentration was measured by an ELISA technique, and urinary albumin excretion was calculated as urinary albumin concentration multiplied by the diuresis. Urinary creatinine concentration was measured by a colorimetric method, and renal clearance of creatinine was calculated as the ratio of urine to serum concentration multiplied by the diuresis and was adjusted for body surface area as calculated by this formula: 

\[ \text{Creatinine clearance} = \frac{\text{Urine creatinine concentration} \times \text{Urine flow}}{\text{Serum creatinine concentration}} \]

and was taken as an index of glomerular filtration rate.

Follow-Up
All participants were followed until December 31, 1998, with respect to development of CHD (ICD-10 codes I20.0 through I25.9) and until August 31, 2001, with respect to death or emigration by means of the National Patient Register, National Register of Causes of Death, and Civil Registration System. The completeness of case finding from the sample was > 95%.24

Statistical Analysis
Differences in baseline characteristics between groups were compared by Student’s t test and the χ² test. RRs were calculated as hazard ratios by Cox proportional-hazards regression analysis with age as the underlying time scale, thereby adjusting for age in all analyses. We also included renal function, diabetes, and hypertension in the analysis because these factors are known to be correlated to urinary albumin excretion, as well as CHD and death. Furthermore, we included plasma concentrations of total cholesterol and HDL cholesterol. Probability values < 5% were taken as significant.

Results
During follow-up, 109 incident cases of CHD and 276 deaths were identified. They were at baseline characterized by higher levels of the conventional atherosclerotic risk factors (Table 1). Furthermore, subjects who developed CHD during follow-up had higher urinary albumin excretion than control subjects [geometric mean, 5.2 μg/min (95% CI, 4.1 to 6.7) versus 3.4 μg/min (3.3 to 3.5); P < 0.0001]. This was also the case among subjects who died [geometric mean, 5.4 μg/min (95% CI, 4.7 to 6.3) versus 3.3 μg/min (95% CI, 3.2 to 3.4; P < 0.0001; Table 1)].

The Figure shows the age- and sex-adjusted RRs of CHD and death according to interquartile intervals of urinary albumin excretion. The risk of both CHD and death was significantly increased if urinary albumin excretion was above the upper quartile (ie, 4.8 μg/min). In subsequent analyses, we therefore

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**TABLE 1. Baseline Characteristics of the Third Copenhagen City Heart Study Population in 1992–1994 Divided Into Individuals Who Developed CHD and/or Died During Follow-Up and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects for CHD</th>
<th>CHD (n = 109)</th>
<th>Control Subjects for Death</th>
<th>Death (n = 276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>45 (43–47)</td>
<td>57 (48–66)‡</td>
<td>44 (42–46)</td>
<td>59 (53–65)‡</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.0 (54.6–55.4)</td>
<td>61.5 (60.3–62.7)*</td>
<td>54.6 (52.5–55.0)</td>
<td>61.2 (60.4–62.0)*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136 (135–137)</td>
<td>145 (141–150)*</td>
<td>135 (134–136)</td>
<td>145 (142–148)*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>86 (85–87)</td>
<td>89 (86–91)¶</td>
<td>86 (85–87)</td>
<td>89 (87–90)*</td>
</tr>
<tr>
<td>Antihypertensive medicine, %</td>
<td>8 (7–9)</td>
<td>27 (19–35)*</td>
<td>8 (7–9)</td>
<td>18 (13–23)‡</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>49 (47–51)</td>
<td>58 (49–67)‡</td>
<td>48 (46–50)</td>
<td>66 (60–72)‡</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7 (25.5–25.9)</td>
<td>26.8 (26.0–27.6)§</td>
<td>25.7 (25.5–25.9)</td>
<td>26.3 (25.8–26.8)§</td>
</tr>
<tr>
<td>Diabetics, %</td>
<td>2.8 (2.2–3.4)</td>
<td>10.1 (4.4–15.8)§</td>
<td>2.5 (1.9–3.1)</td>
<td>9.1 (5.7–14.5)‡</td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L</td>
<td>6.2 (6.1–6.3)</td>
<td>6.6 (6.4–6.9)†</td>
<td>6.2 (6.1–6.3)</td>
<td>6.3 (6.1–6.5)</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mmol/L</td>
<td>1.58 (1.56–1.60)</td>
<td>1.43 (1.33–1.52)‡</td>
<td>1.57 (1.56–1.59)</td>
<td>1.54 (1.47–1.61)</td>
</tr>
<tr>
<td>Renal creatinine clearance, mL/(min×m²)</td>
<td>43 (42–44)</td>
<td>41 (38–44)</td>
<td>42 (39–44)</td>
<td>40 (39–42)§</td>
</tr>
<tr>
<td>Urine albumin excretion, μg/min</td>
<td>3.4 (3.3–3.5)</td>
<td>5.2 (4.1–6.7)†</td>
<td>3.3 (3.2–3.4)</td>
<td>5.4 (4.7–6.3)*</td>
</tr>
</tbody>
</table>

Values in parentheses indicate 95% CIs. Continuous variables are given as means, except for urine albumin excretion, which is given as geometric mean.

* P < 0.0001; † P < 0.005; ‡ P < 0.0005; § P < 0.001; ¶ P < 0.05 vs control subjects.
defined microalbuminuria as a urinary albumin excretion >4.8 μg/min. For comparison, we also analyzed the risk associated with urinary albumin excretion >15 μg/min (ie, the cutoff level used among diabetes patients).

Urinary albumin excretion >4.8 μg/min was associated with a significantly increased risk of CHD and death of ~2 in both men and women, and it was mainly unaffected by adjustment for age, creatinine clearance, hypertension, diabetes, and total and HDL cholesterol (Table 2). Urinary albumin excretion >15 μg/min was also associated with a significantly increased risk of death of ~3 in both men and women regardless of age, creatinine clearance, hypertension, diabetes, and total and HDL cholesterol. This was also the case regarding CHD in men, whereas the risk of CHD in women was not increased significantly when urinary albumin excretion was >15 μg/min (Table 2).

Discussion

This prospective population study of 2762 men and women 30 to 70 years of age with a 7- to 9-year follow-up has confirmed the results from previous reports of increased risk of CHD and death associated with small amounts of albumin excreted in the urine, ie, microalbuminuria.12,14,23-29 To specify the risk level of urinary albumin excretion in a simple manner with sufficient statistical power and without any presumptions, we stratified the population according to quartiles of urinary albumin excretion. Thus, the major novel observation in the present study was that a urinary albumin excretion rate exceeding only 4.8 μg/min (corresponding to ~6.4 μg/min during daytime)30 strongly predicts CHD and death, and the predictive effect is independent of age, sex, renal function, diabetes, hypertension, and lipids. Furthermore, because of the pronounced intravascular individuality of urinary albumin excretion and thus regression dilution,31 the estimated risks of CHD and death associated with microalbuminuria may be underestimated.

Data from the recent HOPE study suggested that any level of microalbuminuria predicts CHD in individuals with or without diabetes.32 The risk increased with the ratio of urinary albumin to creatinine concentration, starting well below the usually defined level of microalbuminuria, as in our study. Thus, the HOPE study suggested that a 0.4-mg/mmol increase in the ratio of urinary albumin to creatinine concentration led to a 5.9% higher age- and sex-adjusted risk of CHD.32 In contrast, we observed in our study that the risk of CHD and death remarkably increased when a 4.8-μg/min threshold of urinary albumin excretion was exceeded. Among diabetes patients, microalbuminuria is usually defined as an albumin excretion of 15 to 150 μg/min in a urine sample collected during night,1 although the risk of CHD and death may be increased at even lower levels.8,32,33 This definition is of limited clinical relevance as a cardiovascular risk factor in the general population. First, <3% of the healthy population has urinary albumin excretion in this range.34 Second, the risk of CHD among women with urinary albumin excretion >15 μg/min was not significantly increased in the present study, perhaps because of insufficient power. The traditional definition of microalbuminuria1 is based on the level of urinary albumin excretion in patients with diabetes that predicts the development of clinical diabetic nephropathy. We suggest the definition be revised according to the level that increases the risk of CHD and death in the general population. In the present study, this level was found to be ~5 μg/min, corresponding to an albumin concentration of ~6 mg/L and an albumin-to-creatinine ratio of ~0.7 mg/mmol in a morning urine sample (data not shown). This cutoff level has also been suggested from previous population studies using the albumin-to-creatinine ratio in a spot urine sample,14,23 which may be a more practical approach in clinical practice. We recognize that many additional factors potentially may influence the urinary albumin excretion in a population study, eg, response rate, population size, age range, frequency of urinary tract infection, and urine collection and examination methods. Despite these factors, the presence of microalbuminuria in a single urine sample seems to increase the risk.14

A prior study has shown that reduced renal creatinine clearance is an independent predictor of CHD in middle-aged subjects.25 We therefore adjusted the association between microalbuminuria and risk of CHD and death for renal creatinine clearance. We found no confounding influence of renal creatinine clearance on the association.

We have previously proposed that microalbuminuria may reflect a systemic transvascular leakiness of macromolecules, including albumin and lipoproteins.1-7,35,36 In a recent study,
however, we were unable to support this hypothesis in both diabetic and nondiabetic individuals (J.S. Jensen et al, unpublished data, 2004). It is likely that microalbuminuria emerges later in the atherosclerotic process.37–39 Intervention trials against, for example, modifiable risk factors in persons with microalbuminuria would be of relevance to obtain further evidence for screening for microalbuminuria in the population.

In conclusion, microalbuminuria is a strong determinant of CHD and death independently of age, sex, hypertension, diabetes mellitus, renal function, and lipids. From these observations, we suggest changing the usual definition of microalbuminuria, ie, urinary albumin excretion >15 μg/min (in nocturnal collections), to >5 μg/min (or albumin-to-creatinine ratio >0.7 mg/mmol) and including it in the individual risk assessment of atherosclerotic cardiovascular disease.

Acknowledgments
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References
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