Urinary Albumin Excretion
An Independent Predictor of Ischemic Heart Disease

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Abstract—Cross-sectional studies suggest that an increased urinary albumin excretion rate is associated with cardiovascular disease, dyslipidemia, and hypertension. The purpose of this study was to analyze prospectively whether the urinary albumin-to-creatinine (A/C) ratio can independently predict ischemic heart disease (IHD) in a population-based cohort. In 1983, urinary albumin and creatinine levels were measured, along with the conventional atherosclerotic risk factors, in 2085 consecutive participants without IHD, renal disease, urinary tract infection, or diabetes mellitus. The participants were followed up until death, emigration, or December 31, 1993. IHD was defined as a hospital discharge diagnosis or cause of death including the diagnosis ICD-8 and 410 to 414. Seventy-nine individuals developed IHD during the 21 130 person-years of follow-up. They were characterized by a preponderance of males and higher age, body mass index, blood pressure, lipoproteins, and proportion of current smokers. Microalbuminuria was defined as an A/C ratio >90 percentile (>0.65 mg/mmol). When adjusted for other risk factors, the relative risk of IHD associated with microalbuminuria was 2.3 (95% CI, 1.3 to 3.9, P=0.002), and the 10-year disease-free survival decreased from 97% to 91% (P<0.0001) when microalbuminuria was present. An interaction between microalbuminuria and smoking was observed, and the presence of microalbuminuria more than doubled the predictive effect of the conventional atherosclerotic risk factors for development of IHD. It is concluded that microalbuminuria is not only an independent predictor of IHD but also substantially increases the risk associated with other established risk factors. (Arterioscler Thromb Vasc Biol. 1999;19:1992-1997.)

Key Words: urinary albumin excretion ■ microalbuminuria ■ ischemic heart disease ■ atherosclerosis

Microalbuminuria, ie, slightly elevated urinary albumin excretion, was initially demonstrated in patients with diabetes mellitus, where it was shown to be associated with atherogenic changes in the cardiovascular risk profile,1,2 and to predict increased mortality and cardiovascular disease.3–12 Several studies have demonstrated an association between slightly increased urinary albumin excretion and cardiovascular risk factors, even in the general population.13–19 In the Copenhagen City Heart Study, we found that otherwise-healthy individuals with a urinary albumin excretion level >90th percentile (>7 µg/min) were characterized by higher blood pressures and lower plasma concentrations of apolipoprotein A-1 and HDL cholesterol.20 Furthermore, they had a generalized transvascular leakiness for albumin.21 These observations suggest that individuals with slightly increased urinary albumin excretion may be at increased risk for the subsequent development of ischemic heart disease (IHD). The pathogenic mechanisms leading to increased risk are still unknown, but microalbuminuria has been suggested as a marker of endothelial dysfunction and hyperpermeability to macromolecules,22,23 which occurs early in atherogenesis.24 In 1995 Kuusisto et al25 showed that in elderly (mean age, 69 years), nondiabetic individuals who were followed up for 3.5 years, microalbuminuria was a marker for subsequent development of coronary heart disease. This was particularly evident in patients with hyperinsulinemia. These authors defined microalbuminuria as a urinary A/C ratio exceeding that for the upper quintile of the entire population under study (A/C ratio >3.22 mg/mmol, corresponding to a urinary albumin excretion well above 20 µg/min). This excretion rate is high for nondiabetic individuals compared with our data.26,27 and data from other, predominantly population-based studies.13–19,28

In the present study, we followed our previous definition of microalbuminuria for the nondiabetic population,20,21,26,27 ie, urinary albumin excretion >90th percentile. With this definition, the aim of our study was to 1) analyze whether microalbuminuria predicts subsequent development of IHD (IHD) in young and middle-aged individuals (30 to 60 years) and ii) study the interaction between microalbuminuria and established atherosclerotic risk factors in the prediction of IHD.

Methods

Study Population

The World Health Organization (WHO) MONICA study (Monitoring Trends and Determinants of Cardiovascular Diseases) is a

Received August 20, 1998; revision accepted November 24, 1998.

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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

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10-year study in geographically defined populations. More than 100,000 randomly selected individuals from 38 centers are participating. From April 1982 to February 1984, the first Danish MONICA survey was performed at the Glostrup Population Studies center. We invited a total of 4807 individuals born in 1922, 1932, 1942, or 1952 (an equal number of males and females from each stratum) representing a random sample from 11 municipalities surrounding Glostrup University Hospital in Copenhagen County. A total of 3785 individuals (79%) participated in the survey. The sampling region is representative of Denmark with respect to income, level of education, and socioeconomic status but with underrepresentation of farmers and fishermen and a small excess of unskilled workers. A self-administered questionnaire was mailed to the participants before the examination. The population has been described in detail elsewhere. Urine samples were collected from February 7, 1983 and continued until the end of the survey. Thus, among the 3785 individuals participating in the MONICA survey 2782 consecutive participants were included in the present study. Because participants were invited in random order, the subgroup with urine samples comprised a random sample of all participants.

Atherosclerotic Risk Factors

Fasting blood samples were drawn for measurement of plasma total cholesterol, HDL cholesterol, and plasma triglycerides (enzymatic colorimetric methods: CHOL CHOD-PAP, HDL cholesterol precipitant, and GPO-PAP, respectively; Peridichrom, Boehringer Mannheim GmbH). Blood glucose was not measured. Blood pressure was measured 3 times to the nearest 2 mm Hg in sitting position with use of a London School of Hygiene sphygmomanometer and an appropriately sized cuff. Height and weight were measured. As part of a different subproject, all individuals underwent ultrasound examination of both kidneys and the urinary tract.

Microalbuminuria

Urine samples were collected as first morning spot urine samples. After a dip-stick test, aliquots were stored at −20°C for the following 11 to 12 years. Urine analyses for albumin and creatinine concentrations were performed in 1995. Urinary albumin was measured using an ELISA-technique (dilution 1:100; lower detection limit, 0.1 mg/l; interassay CV, 8.3%; intra-assay CV, 2.1%). We defined the lower 90% range of the albumin-to-creatinine ratio as normal and the upper 10% (corresponding to an A/C ratio >0.65 mg/mmol) as abnormal. This definition is in accordance with recent recommendations. Individuals were excluded if they had IHD, diabetes, glucosuria, hematuria (by urinary dip-stick-test), history of renal disease, history of urinary tract infection within 3 months of entry to the study, or an abnormal ultrasonic examination of the kidneys or urinary tract at baseline. Diabetes was classified as yes/no based on the questionnaire item, “Has a doctor ever told you that you suffer from diabetes?”

Ischemic Heart Disease

Based on the Danish personal identification code (so-called CPRnumber), all individuals were followed up until death, emigration, or December 31, 1993. Information on vital status, cause of death, hospital admissions, and diagnoses were traced in national registers. We identified all cases with fatal or nonfatal myocardial infarction, angina pectoris, or IHD (ICD-8 code No. 410 to 414). Studies of the validity of the Danish Hospital Discharge Register have shown that between 89% and 99% of clinically manifest myocardial infarctions are registered.

Statistical Analysis

Baseline characteristics in the patients developing IHD and those not developing IHD were compared using Student’s t test or the χ² test. The effect of the baseline parameters on the risk of developing IHD was analyzed by Cox proportional-hazards regression analysis with the conditional forward selection procedure. The free from IHD survival during follow-up for individuals in the lower 90% range and upper 10% of urinary A/C-ratio was compared with a Kaplan-Meier plot and log-rank test statistics. All variables independently predicting the development of IHD (P<0.05) were tested for interaction with microalbuminuria on the risk of IHD. The graphical presentations given in Figures 2a through 2e are all based on combinations of the combined effect of microalbuminuria and the second risk factor, adjusted for the effect of all remaining risk factors (ie, age, sex, body mass index, systolic blood pressure, smoking, cholesterol [total and HDL], and triglycerides). In the categorical analyses, systolic blood pressure was categorized as normal (<140 mm Hg), borderline (140 to 160 mm Hg), or hypertensive (>160 mm Hg) according to the recommendations from WHO. Cholesterol was categorized as normal (<5.2 mmol/L), slightly elevated (5.2 to 7.0 mmol/L), or high (>7.0 mmol/L). These cutoff levels were chosen on the basis existing intervention studies, where 5.2 corresponded to the treat-ment target in the 4S Study and 7.0 corresponded to the high level in the West of Scotland trial. HDL was categorized as low (<0.9 mmol/L), intermediate (0.9 to 1.5 mmol/L), or high (>1.5 mmol/L). The analyses were performed by the statistical software package SPSS for Windows, version 6.0.

Results

In total, urine samples were collected from 2782 Of these, 69 were excluded because of diabetes or glucosuria and 551 because of a history of urinary tract infection, abnormal ultrasonic examination, or microscopic hematuria. This left 2181 individuals for follow-up. Among these, 96 had previous definite or possible IHD but with an uncertain time of onset. Consequently, they were excluded from the analysis because they did not represent incident cases during follow-up. Seventy-nine individuals developed IHD during follow-up (incident cases). Table 1 shows the clinical characteristics of the entire study population. Individuals subsequently developing IHD were characterized by male preponderance (76% versus 54%); a higher A/C ratio (0.25 versus 0.18 mg/mmol), blood pressure (133/79 versus 120/72 mm Hg); prevalence of current smokers (77% versus 55%); and an older age distribution (age ratio percentages of

| TABLE 1. Baseline Characteristics of the Study Population (N=2085) |
|-------------------|-------------|-------------------------------|-----------------|
|                  | Proportion  | Mean                          | 95% CI           |
| Male, %           | 55          | 53–57                          |                 |
| Age, %            |             |                               |                 |
| 30 y              | 29          | 27–31                          |                 |
| 40 y              | 28          | 26–30                          |                 |
| 50 y              | 25          | 23–27                          |                 |
| 60 y              | 18          | 16–20                          |                 |
| Urine A/C, mg/mmol| 0.18*       | 0.17–0.19                      | 0.03–1.03       |
| Systolic blood pressure, mm Hg | 121 | 120–122 | 101–149 |
| Diastolic blood pressure, mm Hg | 72 | 71–73 | 57–90 |
| Body mass index, kg/m² | 24.6 | 24.4–24.8 | 19.5–31.4 |
| Plasma total cholesterol, mmol/L | 6.0 | 5.9–6.1 | 4.3–8.1 |
| Plasma HDL cholesterol, mmol/L | 1.51 | 1.49–1.53 | 0.92–2.29 |
| Plasma triglycerides, mmol/L | 1.14* | 1.12–1.17 | 0.56–2.83 |
| Smokers at baseline, % | 56 | 54–58 |

*Geometric mean.
subjects who were 30/40/50/60, (2%/10%/37%/51% versus 20%/28%/25%/17%). All of these differences were significant ($P<0.01$).

Table 2 shows the results of the Cox-regression analyses. Microalbuminuria was associated with a 2.3-fold increased risk of IHD compared with normoalbuminuric individuals. This effect is of the same magnitude as that for male sex, high age (10-year increase), and current smoking. When the RR of IHD was compared in dec, corrected for the effect of other risk factors and after Bonferroni correction for multiple testing; the risk of IHD did not increase further with higher levels of the A/C ratio.

As shown in Figure 1, the crude survival free from IHD during follow-up among normoalbuminuric individuals was 97% compared with 91% in the group with microalbuminuria ($P<0.0001$). After adjusting for the effects of age, sex, smoking, blood pressure, total cholesterol, HDL cholesterol, triglycerides, and body mass index, the 10-year disease-free survival was 99% and 97% in the 2 groups, respectively ($P=0.005$). This decrease in risk difference was mainly due to older age and higher blood pressures in the subjects developing IHD.

Figure 2a through 2e shows the combined effect of microalbuminuria and each of the other significant risk factors. Each panel has been adjusted for the effect of all other significant risk factors. A/C ratio and sex both contributed to the risk of IHD (Figure 2a), but no significant interaction between the 2 variables was found. Thus, males with microalbuminuria had a risk of IHD 5.1 times higher than normoalbuminuric females.

The combined effect of smoking and microalbuminuria is shown in Figure 2b. In nonsmokers, microalbuminuria alone did not have a significant effect, but there was a significant interaction between smoking and microalbuminuria ($P<0.01$). Thus, smoking alone was associated with a RR of IHD of 2.5 in normoalbuminuric individuals but 5.6 in smokers with microalbuminuria.

Elevated systolic blood pressure (Figure 2c) and microalbuminuria both conferred an increased risk of IHD. This was the case for mild hypertension (systolic blood pressure 141 to 160 mm Hg) as well as for more severe hypertension (>160 mm Hg), where the combined effect of hypertension and microalbuminuria was increased 3.3 times and 5.3 times, respectively.

For total and HDL cholesterol, an effect of lipid levels as well as microalbuminuria was observed (Figure 2d and 2e). The combined effect of cholesterol >7.0 mmol/L and microalbuminuria was an RR for IHD of 10.5 compared with normoalbuminuric individuals with a total-cholesterol level <5.2 mmol/L. HDL cholesterol <0.9 mmol/L with microalbuminuria was associated with an RR of 6.1 compared with normoalbuminuric individuals with HDL cholesterol >1.5 mmol/L.

**Discussion**

In this population-based study, we have demonstrated that a urinary A/C ratio in the upper 10% range is independently associated with an increased risk of developing fatal or nonfatal IHD. This result confirms previous observations in patients with diabetes mellitus$^{5,6}$ and shows that microalbuminuria is a potent marker for an increased risk of IHD in nondiabetic populations also. Three previous studies have reported similar findings.$^{41-43}$ The study by Yudkin et al in 1988$^{41}$ demonstrated that microalbuminuria (using the definition of microalbuminuria from diabetology$^{44}$) was associated with a 24-fold increased mortality rate. This high level of urinary albumin excretion, of 30 mg/24 h or more, is, however, rare in the nondiabetic population$^{26-28}$ and therefore of limited clinical relevance. Damsgaard et al in 1990 found that urinary albumin excretion exceeding only 7.5 µg/min was associated with an increased all-cause mortality.$^{52}$ None of these studies reported a direct association with the development of cardiovascular disease, as had been found in patients with diabetes mellitus. This was, however, done in a
Figure 2. RRs and (95% CIs) of IHD for combinations of risk factors, adjusted for the effect of all other risk factors. (Microalbuminuria = upper 10% of the distribution of urinary A/C ratio.) a, Sex and microalbuminuria ($P = 0.57$ for interaction); b, smoking and microalbuminuria ($P = 0.009$ for interaction); c, systolic hypertension and microalbuminuria ($P = 0.54$ for interaction); d, total cholesterol and microalbuminuria ($P = 0.79$ for interaction); and e, HDL cholesterol and microalbuminuria ($P = 0.27$ for interaction).
case-control study of women conducted by Gorgels et al., who observed a 1.6 times increased risk of IHD associated with an A/C ratio >0.4 mg/mmol.

On the basis of findings in patients with insulin-dependent or non–insulin-dependent diabetes mellitus, we had previously advanced the hypothesis that microalbuminuria is a marker of a generalized vascular dysfunction (the “Steno Hypothesis”). In recent years, elevated urinary albumin excretion has been also demonstrated in nondiabetic individuals, and it has been found to be associated with elevated blood pressure, dyslipidemia, and high plasma insulin levels. Hypertension and dyslipidemia are both well-established risk factors for the development of cardiovascular disease. Furthermore, in a cross-sectional, population-based study of >2600 individuals from the Copenhagen City Heart Study, we have demonstrated that microalbuminuria is associated with the prevalence of cardiovascular disease.

In the present study, we found that microalbuminuria is a predictor of the development of IHD, independent of other established atherosclerotic risk factors such as male sex, arterial hypertension, dyslipidemia, smoking, old age, and obesity. The general effect of microalbuminuria in this study was that the risk associated with conventional risk factors was more than doubled when the individual had microalbuminuria as well. The specific pathogenic mechanisms behind this association are still poorly understood. We have previously shown that healthy individuals with microalbuminuria have a generalized increase in transvascular escape of albumin. In animals, increased transvascular albumin transport is associated with an increased transport of lipoproteins into the arterial wall, and therefore we speculated that microalbuminuria might be a marker of increased susceptibility to the atherogenic effect of other established risk factors rather than a classic risk factor per se (ie, directly involved in the pathogenic mechanism). However, no significant interaction was observed between microalbuminuria and dyslipidemia for the development of IHD in this study.

In the present study, we used the urinary A/C ratio as a marker of albumin excretion rate. The classic definition of microalbuminuria was established in diabetology on the basis of the cut-off level that predicted the development of diabetic nephropathy (ie, >30 mg/24 h). For screening purposes in population-based studies, collection of 24-hour urine samples would be difficult or almost impossible. In a previous study, we used overnight urine sampling, but even with this protocol we had an ~50% dropout rate in a population-based survey. In the present study, we used a spot urine collection to increase compliance. Because albumin concentration in the urine is affected by the level of diuresis, we adjusted for this by dividing albumin concentrations by urinary creatinine concentration. Investigating microalbuminuria with the A/C ratio is less precise than using the albumin excretion rate per se in urine, thereby detracting from the possibility of demonstrating a positive association. Also, we used only 1 urine sample to classify our individuals. With an intra-individual day-to-day variability in albumin excretion of 25% to 40%, this gives a high for random misclassification, further reducing the chance of detecting a positive association. In the present study, we collected the urine samples in 1983 to 1984. The samples were stored at -20°C for >10 years before analysis. Long-term storage of urine samples will cause some degradation of albumin. Previously, we had shown that over a period of 15 months, the relative degree of degradation is independent of the initial albumin concentration. In the present study, we analyzed the effect of urinary A/C ratio based on the relative ranking in deciles; thus, degradation of albumin should not affect our results. It should, however, be noted that the urinary A/C ratios at entry into the study were likely than the values given in the present investigation.

In this study as well as in our previous work, we defined microalbuminuria as a urinary albumin excretion exceeding the upper 90th percentile of the distribution in the general population. This definition differs from the conventional definition in diabetology, ie, a urinary albumin excretion exceeding 30 mg/24 h, or 20 µg/min. Even in diabetic patients, the risk of developing cardiovascular disease probably increases at lower levels of urinary albumin excretion. In the nondiabetic population, microalbuminuria would primarily be of interest as a potential predictor of macrovascular disease, not renal disease. Our aim was to study whether slightly elevated urinary albumin excretion might be a clinically relevant risk marker for development of IHD. Because we found that the increased risk of IHD was confined to the upper decile of urinary albumin excretion, we have shown that this cut-off level represents the clinically relevant definition of microalbuminuria in the general population. Owing to the long storage of the urine samples we are not, however, able to identify the exact “at-risk level” of the A/C ratio.

This population-based study demonstrated that a slightly increased urinary A/C ratio is a potent and clinically relevant risk marker for the development of IHD. Because microalbuminuria predicts IHD independently of other classic atherosclerotic risk factors and moreover, interacts with the effect of smoking, this suggests that an increased atherogenic susceptibility is conferred. Thus, individuals with other atherosclerotic risk factors such as smoking, dyslipidemia, and hypertension should have their urinary albumin excretion measured, because this piece of information contributes to the classification of the individual as a high-risk or high-susceptibility individual. It is unknown whether individuals with microalbuminuria also will benefit more from intervention, but we would recommend that future controlled clinical trials should focus on answering this question, as it could lead to a more targeted and focused strategy for the prevention of IHD.

Acknowledgments

This study was supported by grants from the Danish Medical Research Council (No. J 12-2008-1) and the Danish Heart Foundation.

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doi: 10.1161/01.ATV.19.8.1992
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/19/8/1992

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