Urinary Albumin Excretion as a Predictor of the Development of Hypertension in the General Population

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The hypothesis that high urinary albumin excretion (UAE; indicating mild renal damage) may precede development of hypertension was tested, and the relation among UAE, GFR, and development of hypertension was investigated. Data of 4635 patients of a prospective cohort study who participated in an extensive screening in 1997 to 1998 and 2001 to 2003 at our outpatient unit and were normotensive at baseline were used. Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria, UAE was measured in two consecutive 24-h urine samples, and GFR was calculated with the modified Modification of Diet in Renal Disease formula. Mean follow-up was 4.3 yr. Baseline UAE was significantly associated with the risk for developing hypertension (odds ratio 2.29; 95% confidence interval 1.77 to 2.95 per 10-fold increase of UAE). This association was independent of potential confounders. An interaction between UAE and GFR was found ($P = 0.030$), indicating that with elevated UAE and lowered GFR, but still within the normal range, the risk for developing hypertension was highest. In conclusion, these findings support the hypothesis that mild renal damage may precede the development of hypertension.

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BP is thought to be an important determinant of development of high urinary albumin excretion (UAE), an early marker of renal damage (1–3). However, experimental data showed that subtle renal damage in normotensive rats leads to the development of salt-sensitive hypertension (4–6). This suggests that instead of being a consequence of high BP, mild renal damage and, consequently, high UAE also may precede development of hypertension. This is in line with the hypothesis proposed by Goldblatt (7) more than 50 yr ago. On the basis of the observation that in hypertensive individuals arteriolosclerosis of the kidneys is nearly universal but in other organs occurs only in a minority of patients, he suggested that renal damage precedes the development of hypertension. Indeed, this is seen clearly in patients with severe renal impairment, in whom disturbances in volume homeostasis may cause hypertension (1). However, the relation between mild renal damage and development of hypertension in humans is still unknown. We therefore investigated whether an increase in UAE may precede development of hypertension and whether this is due to the association of UAE with renal damage, using a large, community-based, prospective cohort study.

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Materials and Methods

Study Design and Population

This study is part of the ongoing PREVEND study (Prevention of REnal and Vascular ENd stage Disease), a large prospective cohort study that is investigating the predictive value of UAE for renal and cardiovascular disease progression. The patients of the PREVEND cohort were selected in 1997 from 40,856 individuals from the general population. Selection was based on their albumin concentration in a spot morning urine sample to enrich the cohort for the presence of albuminuria. In total, 8592 individuals completed the first survey (1997 to 1998) (8,9). During follow-up, 240 individuals died and 1458 individuals declined participation. Thus, 6894 individuals completed the second survey (2001 to 2003). We used data of the 4635 individuals who did not have hypertension ($n = 2247$) or self-reported renal disease ($n = 12$) at baseline and participated in the first and second surveys. The PREVEND study is approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the declaration of Helsinki. All participants gave written informed consent.

Measurements and Definitions

For each screening, participants completed two visits at our outpatient unit. Height, weight, and waist circumference were measured. Participants completed a questionnaire on demographics, cardiovascular and renal disease history, and use of medication for hypertension. Information on drug use was complemented with data from community pharmacies. During the first and second visits, BP was measured at the right arm, in supine position, every minute for 10 and 8 min, respectively, with an automatic device (Dinamap XL Model 9300; Johnson-Johnson Medical, Tampa, FL). Two 24-h urine samples were collected after thorough oral and written instructions on how to perform a urine collection, and a fasting blood sample was drawn. Standard 12-lead electrocardiograms were recorded with Cardio Perfect equip-

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ment (Cardio Control, Rijswijk, The Netherlands) and stored digitally using the computer program MEANS (Modular Electrocardiogram ANalysis System).

Urinary albumin concentration was determined by nephelometry (BNII; Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-h urine excretions. Concentrations of sodium, high-sensitivity C-reactive protein (hs-CRP), creatinine, total cholesterol, triglycerides, insulin, and glucose were measured in serum or urine using standard methods.

BP values are given as the mean of the last two recordings of both visits. Hypertension was defined as a systolic BP (SBP) of ≥140 mmHg and/or a diastolic BP (DBP) of ≥90 mmHg and/or the use of antihypertensive medication according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (10). GFR was estimated with the modified Modification of Diet in Renal Disease formula, taking into account gender, age, race, and serum creatinine concentration (1). Sodium intake was estimated with 24-h urinary sodium excretion. Participants were defined as smoking when they had smoked regularly in the previous year. Increased alcohol use was defined as drinking >3 glasses/d. Left ventricular hypertrophy (LVH) was identified using the Cornell voltage-duration product, calculated as R wave from aVL lead (RaVL) + S wave from V_3 lead (SV_3) (with 6 mm added in women) times QRS duration. A threshold of 2440 mm/ms was used to identify LVH (11).

Statistical Analyses

Analyses were performed using the statistical package SPSS 12.0 (SPSS, Chicago, IL). The level of significance was determined as $P < 0.05$. Continuous data are reported as mean with SD or as median and interquartile range in case of a skewed distribution. Prevalence and incidence are presented as percentages. Differences between groups were tested by a *t* test or a Mann-Whitney rank test for continuous data with a normal or skewed distribution, respectively. Differences in prevalence or incidence were tested with a χ^2 test. To test for trends in ordinal data, we used the Mantel-Haenszel χ^2 test for trend.

The predictive value of UAE was tested in logistic regression models with development of hypertension as dependent variable. Logarithmic transformation (Ln) of UAE, hs-CRP, insulin, and triglycerides was applied in logistic regression analysis to fulfill the requirement of linearity in the logit. The final multivariate model was tested for interactions. Interactions were considered significant at $P < 0.1$. Models were tested for tolerance to colinearity with methods described by Hosmer *et al.* (12). Data of logistic regression analysis are given as odds ratio (OR) and 95% confidence interval (CI).

Results and Discussion

We observed 19592 person-years during a mean follow-up of 4.2 yr. In this time, 413 (8.9%) participants of our population developed hypertension, giving an incidence rate of 21/1000 person-years. Compared with participants who remained normotensive during follow-up, participants who developed hypertension were generally older, with an unfavorable cardiovascular risk profile, including higher SBP and DBP and decreased GFR (Table 1). UAE was increased in participants who developed hypertension. Accordingly, the incidence of hypertension was higher with higher baseline levels of UAE (Figure 1).

When baseline UAE was entered in a logistic regression model with hypertension as dependent variable, UAE significantly predicted development of hypertension with an OR of

Table 1. Population characteristics[a]

	Newly Diagnosed Hypertension		*P* Value
	No ($n = 4222$)	Yes ($n = 413$)	
Age (yr)	44.5 (10.4)	52.0 (10.6)	<0.001
Male (*n* [%])	1921 (45.5)	194 (47.0)	0.566
White (*n* [%])	4008 (95.5)	401 (97.3)	0.319
BMI (kg/m^2)	24.9 (3.6)	27.1 (4.3)	<0.001
Alcohol >3 units/d (*n* [%])	171 (4.1)	28 (6.8)	0.010
Smoking (*n* [%])	1670 (39.7)	152 (36.9)	0.271
Systolic BP (mmHg)	118 (11)	130 (8)	<0.001
Diastolic BP (mmHg)	69 (7)	76 (7)	<0.001
Cholesterol (mmol/L)	5.5 (1.1)	5.8 (1.1)	<0.001
Triglycerides (mmol/L)	1.0 (0.8 to 1.4)	1.3 (0.9 to 1.8)	<0.001
Fasting glucose (mmol/L)	4.6 (0.8)	4.9 (0.9)	<0.001
Fasting insulin (mU/L)	7.0 (5.1 to 10.0)	8.7 (5.9 to 12.8)	<0.001
Serum creatinine (μmol/L)	82 (12)	83 (15)	0.064
GFR (ml/min per 1.73 m^2)	83 (13)	80 (14)	<0.001
C-reactive protein (mg/L)	0.9 (0.4 to 2.3)	1.5 (0.6 to 3.4)	<0.001
Left ventricular hypertrophy (*n* [%])	132 (3.1)	17 (4.2)	0.271
Urinary sodium excretion (mmol/24 h)	141 (49)	139 (51)	0.371
UAE (mg/24 h)	7.9 (5.8 to 12.1)	9.5 (6.5 to 16.4)	<0.001

[a]Values are given as mean (SD) or median (interquartile range) in case of skewed data distribution. Statistical analyses were performed with *t* test, Mann-Whitney test in case of skewed distribution, or χ^2 test in case of categorical variable. UAE, urinary albumin excretion.

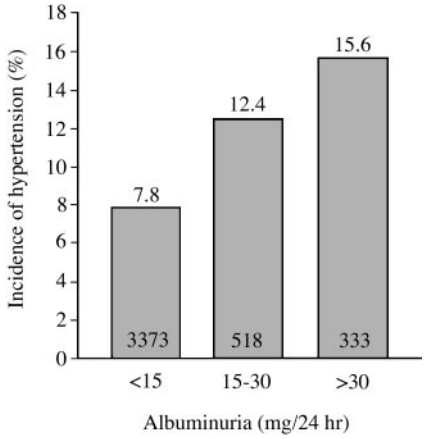

Figure 1. Baseline urinary albumin excretion (UAE) and incidence of hypertension after 4.2 yr of follow-up. Incidence is given according to clinical categories of UAE at baseline ($P < 0.001$ for trend). Numbers in the bars indicate the number of individuals within the category. When we subdivided the population according to tertiles of UAE at baseline (<6.5, 6.5 to 10.5, and >10.5, respectively), a similar trend was seen, with an incidence of hypertension of 6.5, 8.3, and 11.9% from the lowest to the highest tertiles, respectively ($P < 0.001$ for trend).

1.43 (95% CI 1.28 to 1.60) per 1 Ln(UAE) unit of change. This equals an OR of 2.29 (95% CI 1.77 to 2.95) for each 10-fold increase of UAE. After adjustment for age and gender; baseline values of SBP, DBP, and GFR; and other possible confounders, the association between UAE and the development of hypertension remained significant (Table 2).

In the final model, a significant interaction was found between UAE and GFR (Table 2, model 5). To explore this interaction, we repeated our final model in strata according to tertiles of GFR. Results for UAE in the three strata of GFR were OR 1.93 (95% CI 1.26 to 2.97), OR 0.84 (95% CI 0.41 to 1.71), and OR 1.16 (95% CI 0.54 to 2.49) per 10-fold increase of UAE in the lowest to highest tertiles, respectively. The interaction between UAE and GFR is illustrated in Figure 2. This graph shows that UAE predicts the development of hypertension most strongly when renal function is low, indicating synergism. When renal function is higher, the risk that is added by an increased UAE diminishes.

These findings are in contrast with current thinking that elevated UAE is secondary to development of high BP (2,10). One could argue that our observation is erroneous and caused by the presence of prehypertension in individuals with high UAE at baseline or by misclassification of individuals as normotensive at baseline as a result of variation in the BP measurement, whereas in fact they were hypertensive. Therefore, we first adjusted our models for baseline SBP and DBP. After these adjustments, the association between UAE and development of hypertension remained significant. Second, we repeated our analyses after adjustment for the presence of LVH at baseline. LVH is considered a marker of target organ damage in hypertensive individuals (2,10) and might indicate the presence of prehypertension or undiagnosed hypertension in individuals who are classified as normotensive. However, adjustment for the presence of LVH did not influence our finding that baseline UAE predicts the development of hypertension. Third, we excluded participants who had an SBP ≥135 and/or DBP ≥85 ($n = 505$) at baseline. This cutoff point was chosen to exclude individual who had the highest risk for being prehypertensive or misclassified as normotensive while maintaining an ade-

Table 2. Logistic regression models with development of hypertension after 4.2 yr of follow-up as dependent variable[a]

	OR (95% CI)	*P* Value
Model 1		
ln(UAE)	1.43 (1.28 to 1.60)	<0.001
Model 2		
ln(UAE)	1.36 (1.22 to 1.53)	<0.001
Model 3		
ln(UAE)	1.17 (1.03 to 1.33)	0.003
Model 4		
ln(UAE)	1.18 (1.03 to 1.36)	0.016
Model 5		
ln(UAE)	2.69 (1.27 to 5.72)	0.010
eGFR	1.30 (0.99 to 1.70)	0.055
ln(UAE) × eGFR	0.90 (0.81 to 0.99)	0.030

[a]OR for ln(UAE) is per 1-unit change; OR for eGFR is per 10 ml/min per 1.73 m^2 change; model 1, crude model; model 2, adjusted for age and gender; model 3, model 2 + adjusted for baseline diastolic and systolic BP; model 4, model 3 + adjusted for baseline body mass index, smoking, alcohol use, sodium intake, levels of glucose, insulin, cholesterol, triglycerides, and high-sensitivity C-reactive protein; model 5, model 4 + inclusion of interaction term ln(UAE) × eGFR. OR, odds ratio; CI, confidence interval; ln(UAE), logarithmic transformed value of UAE; eGFR, estimated GFR.

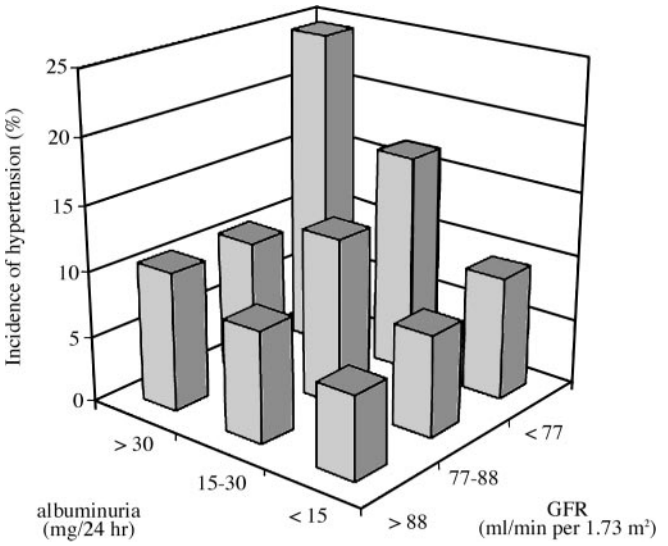

Figure 2. Incidence of hypertension after 4.2 yr of follow-up by categories of albuminuria and tertiles of GFR at baseline.

quate number of cases. Again, this correction did not affect our results. Thus, our study shows that UAE predicts future development of hypertension, independent of other predisposing factors. The increased risk for hypertension associated with elevated UAE is higher when the GFR is lower.

Our results confirm the finding in the Framingham Offspring Study that urinary albumin concentration in a single morning void urine sample is associated with the risk for developing hypertension (13). However, in contrast to our study, the Framingham Offspring Study did not explicitly investigate the relation among UAE, renal function, and development of hypertension. Although the authors added to their statistical model baseline serum creatinine as a renal parameter to adjust for possible confounding by the presence of renal dysfunction, the use of serum creatinine as an estimate of renal function is not recommended (1,14). It is generally accepted that the inverse relation between serum creatinine and GFR is influenced by muscle mass and consequently by factors such as age, gender, and race. These factors should be taken into account using a validated formula.

The finding that baseline UAE predicts BP progression has been debated by the investigators of the HARVEST Study, who were not able to demonstrate such a relation (15,16). This conflicting data may be explained by the lower age of the population in the HARVEST Study (mean age 33 yr), compared with the age of our population (mean age 45 yr) or the population of the Framingham Offspring Study (mean age approximately 55 yr). A different mechanism may underlie the development of UAE in this young age group with low cardiovascular risk, with UAE for instance being more hemodynamically related, whereas UAE may be more associated with renal microvascular damage in the older age groups with higher cardiovascular risk.

We explain our findings as follows. Both lower GFR and higher UAE can have renal damage as the underlying cause (1). Thus, the presence of an interaction between these two variables in our model suggests that UAE predicts the development of hypertension as a result of the underlying presence of mild renal damage. It has been well established that the kidney plays a central role in the pathogenesis of hypertension in case of severe renal function impairment (1,17,18), but even in individuals with mild renal damage, this may be the case. Recent experimental studies in rats have shown that minor changes in the renal microvasculature and tubulointerstitium may lead to salt-sensitive hypertension (4–6), providing a possible pathway whereby mild renal damage can lead to the development of hypertension (19). Furthermore, as hypothesized by Brenner *et al*. (20), a reduction in glomerular filtration surface area, which may be reflected by a mildly reduced GFR, may lead to hypertension as a result of a limited ability to excrete sodium. Indeed, a recent autopsy study suggested that young hypertensive individuals may have a lower number of nephrons than age-matched normotensive control subjects (21), supporting Brenner's hypothesis.

Although the studies mentioned above underscore the importance of the kidney in the pathogenesis of hypertension, the cause of hypertension is heterogeneous. UAE is suggested to be the result of damage to the renal microvasculature (1,22), but these local changes in turn may be part of generalized endothelial dysfunction (23). Indeed, generalized endothelial dysfunction has been suggested to play a role in the cause of hypertension (24,25). Thus, alternatively, the association between UAE and generalized endothelial dysfunction could explain our findings. To test for this possibility, we looked at the effect of hs-CRP on the association among UAE, renal function, and the development of hypertension in our logistic regression models, because hs-CRP has also been found to be associated with generalized endothelial dysfunction (26–28). Although baseline hs-CRP was univariately significantly associated with development of hypertension during follow-up (OR 1.24; 95% CI 1.17 to 1.32 per two-fold change of hs-CRP; $P < 0.001$), in the multivariate models, after adjustment for possible confounders, this association was no longer significant (final model $P = 0.3$). Furthermore, the presence of hs-CRP in the model did not influence the association among UAE, renal function, and the development of hypertension. Thus, in our opinion, it is less likely that the association of UAE with generalized endothelial dysfunction explains our findings.

Strengths of our study are the use of a large community-based cohort, use of 24-h urine samples to estimate UAE, use of data of community pharmacies to complement self-reported data on use of antihypertensive drugs, extensive adjustment for covariates that are associated with development of hypertension, and the possibility to explore different possible pathways to explain the association between UAE and the development of hypertension. Two limitations should be mentioned. First, the PREVEND cohort is selected from a mainly white population. Our findings therefore cannot simply be generalized to other populations. Second, almost 20% of the participants of our baseline cohort died or were not willing to participate during follow-up. Although the differences between baseline characteristics of individuals with follow-up and individuals who were lost to follow-up were numerically small (data not shown), we cannot exclude that survival bias was introduced. However, because individuals with high UAE, lower GFR, or hypertension are more likely to be lost during follow-up as a result of the associated increased morbidity and mortality, it is likely that such a bias has led to an underestimation of the true association among UAE, GFR, and development of hypertension.

Conclusion

We conclude from this prospective, community-based cohort study that UAE predicts the development of hypertension, independent of BP and other widely known risk factors for development of hypertension. Our study suggests that this is explained by the association of UAE with mild renal dysfunction. This study therefore gives epidemiologic evidence in support of the hypothesis that mild renal dysfunction may precede the onset of systemic hypertension.

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