Urinary albumin excretion, blood pressure changes and hypertension incidence in the community: effect modification by kidney function

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ABSTRACT

Background. Both increased albuminuria and reduced kidney function may predict blood pressure (BP) progression in the community, while they exacerbate each other’s effects. We investigated associations and interactions between these two risk factors, BP changes and hypertension incidence in community-dwelling elderly men.

Methods. Observational study from the Uppsala Longitudinal Study of Adult Men, which included 1051 men (all aged 71 years) with assessments on urinary albumin excretion rate (UAER), 24-hour ambulatory BP monitoring (ABPM) and cystatin-C estimated glomerular filtration rate (eGFR). Of these, 574 men attended re-examination after 6 years, and ABPM measurements were again recorded to assess blood pressure changes and hypertension incidence.

Results. UAER was found to be associated with ABPM measurements both at baseline and longitudinally. In longitudinal analysis, there were significant interactions between UAER and kidney function in its association with the changes of systolic BP, mean arterial pressure and pulse pressure. After stratification for renal function state, UAER independently predicted BP changes only in those who had eGFR <60 mL/min/1.73 m². At re-examination, 71 new cases of hypertension were recorded. In multivariable logistic models, similar interactions were observed on hypertension incidence: UAER was an independent predictor of incident hypertension only in those with reduced renal function. These associations were evident also in the subpopulation of non-diabetics and in participants with normal range UAER (<20 µg/min).

Conclusions. In community-dwelling elderly men, UAER associates with BP progression and hypertension incidence, even within the normal range. Concurrent reduction of renal function modifies and exacerbates these associations.

Keywords: albuminuria, ambulatory blood pressure monitoring, chronic kidney disease, hypertension, urinary albumin excretion
INTRODUCTION

Hypertension is highly prevalent among elderly individuals and is a well-documented risk factor for cardiovascular morbidity and mortality in the community [1, 2]. Likewise, chronic kidney disease (CKD) has reached epidemic proportions, affecting >10% of the general population and a much larger proportion of elderly individuals [3]. CKD currently contributes to a tenth of all deaths [3]. CKD is characterized by impaired renal function and/or albuminuria, both of which often coexist and deteriorate in parallel. The prognostic value of combining these two features has been highlighted, but not formally tested, in the most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines (online at http://www.kdigo.org/clinical_practice_guidelines/bp.php).

The kidneys play an essential role in the pathogenesis and maintenance of hypertension [4]. Prior epidemiological studies indicate that a high urinary albumin excretion rate, considered a marker of endothelial dysfunction and glomerular hyperfiltration [5, 6], correlates with risk of incident hypertension and blood pressure (BP) progression [7–11], and is considered a marker of subclinical cardiovascular organ damage in primary hypertension [12]. In parallel, renal insufficiency also seems to associate with the development of hypertension [4]. Thus, an interaction between albuminuria and renal insufficiency on exacerbating hypertension incidence/progression may occur, but previous studies have, so far, offered mixed and inconsistent results [8, 11]. In the current study, we try to shed light into this issue by examining longitudinal associations between baseline urinary albumin excretion rate (UAER) and changes in ambulatory blood pressure monitoring (ABPM) as well as hypertension incidence during 6 years’ follow-up in a community-based sample of elderly men. We specifically tested the hypothesis that concurrent kidney dysfunction modifies and exacerbates these associations.

MATERIALS AND METHODS

Study population

The present study is based on the Uppsala Longitudinal Study of Adult Men (ULSAM) cohort (http://www2.pubcare.uu.se/ULSAM/), when participants were ∼71 years old (examinations performed during 1991–95; n = 1221). In the present analysis, we excluded a total of 170 subjects who were missing UAER, serum cystatin C and/or ABPM data, leaving 1051 men for the cross-sectional analysis. Of these 1051 individuals, 333 died or were lost to follow-up before a re-examination took place 6 years later at which time participants were ∼77 years old. Of the 718 men that attended the re-examination, 144 were excluded due to missing ABPM records, leaving 574 men for the longitudinal analysis. Supplementary Figure S1 depicts the selection of the study population with details regarding specific causes for exclusions. No major characteristics differed between included and non-included participants at re-examination (data not shown). All participants gave written consent, and the Ethics Committee of Uppsala University approved the study. Clinical characteristics of studied subjects at baseline and at re-examination are shown in Supplementary Table S1.

Demographics, comorbidities and laboratory measurements

Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in metres. Smoking status was defined as current smoking versus non-smoking. Regular physical activity was defined as the reporting of regular or athletic leisure-time exercise habits according to four physical activity categories (sedentary, moderate, regular and athletic) [13]. Previous cardiovascular disease (CVD) was defined as history of any CVD as recorded in the Swedish Hospital Discharge Registry [International Classification of Diseases (ICD)-8 codes 390 to 458 or ICD-9 codes 390 to 459]. Hyperlipidaemia was defined as serum cholesterol >6.5 mmol/L, serum triglycerides >2.3 mmol/L or treatment with lipid-lowering medications. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L, 2-h post-load glucose level ≥11.1 mmol/L, or the use of oral hypoglycaemic agents or insulin [14].

Classification of anti-hypertensive drugs was performed according to the, at that time, current list of pharmaceutical specialties available in Sweden (FASS 1992/1993). All information about use of diuretics, α-blockers, β-blockers, calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACEI) was collected with a medical questionnaire.

Serum cystatin C was measured by latex-enhanced reagent (N Latex Cystatin C, Dade Behring, Deerfield, IL, USA) with a Behring BN ProSpec analyser (Dade Behring). Estimated glomerular filtration rate (eGFR) was calculated from serum cystatin C concentrations (milligrams per litre) by the following formula: eGFR = 77.24 × cystatin C $-1.2623$, which has been shown to be closely correlated with iohexol clearance [15]. Renal insufficiency was defined as having a cystatin-C eGFR <60 mL/min/1.73 m² [16]. UAER was calculated on the amount of albumin in the urine collected during the night. The subjects were instructed to void immediately before going to bed and to record the time. All urine samples during the night and the first sample of urine in the morning after rising were collected and used for the analysis. The assay employed a commercially available radioimmunoassay kit (Albumin RIA 100, Pharmacia, and Uppsala, Sweden). The intra-individual CV was 60%. Macroalbuminuria was defined as UAER >200 μg/min, and microalbuminuria as UAER between 20 and 200 μg/min.

Blood pressure assessment

The ABPM device Accutracker II (Suntech Medical Instruments, Raleigh, NC, USA) was used in both examinations and attached to the subjects’ non-dominant arm by a skilled laboratory technician, and BP recordings were made every 20 min over 24 h (daytime: 06:00–23:00, night-time: 23:00–06:00). Data were edited to a limited extent omitting all readings of zero, all heart rate readings <30 beats/min, DBP readings >170 mmHg, SBP >270 and <80 mmHg, and all readings where the difference between SBP and DBP was <10 mmHg.
SBP and DBP were given by the auscultatory device. Mean arterial pressure (MAP) was calculated over the whole measurement period according to the formula MAP = DBP + 1/3 of pulse pressure (PP) calculated as PP = SBP − DBP.

**Statistical analysis**

Values are expressed as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for skewed variables or percentage of total for categorical variables. Study participants were divided into four groups according to quartiles of UAER. The Jonckheere–Terpstra test was used to assess linear trends [17] across these groups.

In cross-sectional analysis, multivariable linear regressions were calculated to determine independent associations between UAER and BP measurements at baseline. UAER was logarithmically transformed with a square root to normalize its skewed distribution. Two sets of models in a hierarchical fashion were investigated: (i) Model 1 considered adjustment for BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR and the use of ACEI; (ii) Model 2 adjusted for BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR and the use of all types of anti-hypertensive drugs including ACEI, CCB, β-blocker, α-blocker and/or diuretics. Data are expressed as regression coefficients (beta) and 95% confidence intervals (CI).

In longitudinal analysis, the following three outcomes were defined a priori: (i) Intra-individual BP changes, defined as changes in BP measurements from baseline to re-examination; (ii) Incidence of hypertension, defined as either average daytime BP from ABPM ≥135/85 mmHg according to new National Institute for Health and Care Excellence Guidance (NICE) [18] and the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) [19] or intake of anti-hypertensive drugs at re-examination; and (iii) because albuminuria per se or via promoting hypertension can increase death hazards [20], we tested the possibility that individuals dying before re-examination would have confounded the associations observed. Thus, we finally considered a composite outcome of death before re-examination, and the de novo incidence of hypertension as defined by ABPM or intake of anti-hypertensive medication at re-examination. For outcomes (ii) and (iii), participants with hypertension (defined as either average daytime BP from ABPM ≥135/85 mmHg or intake of anti-hypertensive drugs) at baseline were excluded from the analyses.

The relations between UAER and BP changes were investigated in two sets of models in multivariable linear regression analysis: (i) Covariance in adjusted Model 1 included BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR, BP (ABPM SBP, DBP, MAP, PP, respectively) and ACEI at baseline; (ii) In adjusted Model 2, we further adjusted for anti-hypertensive drugs at re-examination. As an exploratory analysis, this adjustment aimed at ensuring that results were not concealed by BP lowering treatments at re-examination, since individuals with elevated BP during follow-up were likely to receive anti-hypertensive drugs and this would conversely attenuate BP progression. Multivariable logistic regression models were used to examine the association between UAER and the risks of incidence of hypertension or the composite outcome above described. These models considered the following covariates: BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR and ABPM SBP. Results are shown as odd ratios and 95% CI.

We examined multivariable adjusted models that included interaction terms for UAER (as a continuous variable) and kidney function (as a binomial variable: eGFR ≥ or <60 mL/min/1.73 m²), and performed the analyses after stratification of individuals according to the presence/absence of renal insufficiency. P values for interaction were reported.

Finally, because both diabetic nephropathy and macroalbuminuria per se may have affected our study outcomes, analyses were repeated in non-diabetics and in the subpopulation of subjects with UAER in the normal range (<20 µg/min).

P <0.05 was regarded as significant. Because multiple comparisons were not taken into account, results have to be considered as descriptive. All statistical analyses were performed using the statistical software STATA version 12 (Stata Corporation, College Station, TX, USA).

**RESULTS**

**Cross-sectional analysis**

The vast majority of individuals (n = 880, 84%) presented UAER levels within the normal range (<20 µg/min), while 146 (14%) had microalbuminuria (UAER 20–200 µg/min), and a further 25 (2%) had macroalbuminuria (≥200 µg/min). Clinical characteristics of studied subjects grouped by quartiles of UAER are shown in Table 1. Across increasing UAER quartiles, subjects had a higher BMI as well as a higher prevalence of smoking, history of CVD and diabetes. They also presented with lower physical activity. Whereas eGFR did not vary across increasing UAER quartiles, all measures of ABPM (SBP, DBP, MAP and PP) were increased with increased UAER.

Multivariable regression analyses were fitted to study cross-sectional associations of UAER with ABPM at baseline (Table 2). In fully adjusted models, log₂ of UAER was considered an independent contributor to the variance of ABPM measurement. The strength of these associations was similar in individuals with or without impaired renal function, and no statistically significant interaction terms were noted (all P > 0.05, data not shown). Adjusting for use of single anti-hypertensive drugs (CCB, β-blocker, α-blocker or diuretics) on top of ACEI gave similar results (data not shown). Similar associations were observed in individuals with and without diabetes (Supplementary Table S2), as well as in individuals with normal range UAER (Supplementary Table S3).

**Longitudinal analysis**

After a follow-up period of 6 years, 574 individuals attended a re-examination and underwent ABPM assessments. Multivariable and logistic regression analyses were fitted to study the longitudinal associations of baseline UAER with changes in ABPM assessments.
In Model 1, adjusted for potential confounders, positive association trends were observed between UAER and changes in DBP and MAP (both by ABPM) between study visits. UAER was not associated with changes in ABPM measurements of SBP or PP (Table 3). Significant interaction terms between UAER and the presence of impaired renal function at baseline on the prediction of changes of SBP, MAP and PP (all assessed by ABPM) were observed. After stratification, log2 of UAER was an independent predictor of these changes in subjects with impaired renal function, but not in those with eGFR > 60 mL/min/1.73 m2. In Model 2, further adjustment for the intake of anti-hypertensive medication at re-examination basically yielded similar results slightly improving the strength of the observed associations (Table 3). Similar associations were observed in non-diabetic subjects (n = 498) (Supplementary Table S4). Due to the low number of diabetics attending re-examination (n = 76), this analysis was not performed. In individuals with UAER in the normal range, similar associations were observed between baseline UAER and changes in SBP, DBP and MAP. Although no statistically significant interaction terms between UAER and the presence of impaired renal function on BP changes were observed in this subsample,
DISCUSSIONS

The main finding of our study is the longitudinal association between higher UAER and increase in ABPM and hypertension incidence in a cohort of community-dwelling elderly men. Importantly, the presence of impaired renal function modified and exacerbated these associations. Although these results may be anticipated, the prognostic value of combining these two features has, to the best of our knowledge, not been formally demonstrated before, while it agrees with the most recent KDIGO guidelines. Of additional interest, these associations were also evident at UAER levels below the current diagnostic threshold for microalbuminuria. Although observational in nature, our analysis refutes the notion that albuminuria should merely be considered as a consequence of long-term poorly controlled hypertension and provides additional support for the importance of the complex bi-directional interplay between the kidney and the vascular system.

Our data use the gold standard ABPM for clinical blood pressure measurement to confirm and expand previous cross-sectional surveys showing a positive cross-sectional association between urinary albumin excretion and BP cross-sectional both in the general population [21–23] and in disease-specific populations (such as hypertensive [24] or diabetic [25, 26] or CKD subjects [27, 28]). In addition, our data also confirm and
expand previous reports describing an association between low-grade albuminuria and incidence of hypertension as diagnosed by office BP [7–11]. Two of these reports explored, as secondary outcome, the potential interaction between albuminuria and kidney function on hypertension incidence, offering mixed and inconsistent results [8, 11]. A possible explanation for these inconsistent results is that eGFR in those two preceding studies were within the normal range (≥60 ml/min/m²). Our study therefore presents the novelty of addressing this issue using the gold standard ABPM technique and analysing both hypertension incidence and ambulatory BP progression in elderly community-dwelling individuals. In our analysis, a large proportion (nearly 50%) of individuals presented moderately compromised kidney function, consistent with the age-prevalence of the population considered. In this setting, we report a consistent longitudinal association between UAER, BP changes and hypertension incidence, and an important effect modification by underlying kidney disease. ABPM has numerous advantages over office BP, as it can avoid the problems of ‘white-coat’ hypertension and circadian BP variability, reduce misdiagnosis and provide better information regarding target organ injury and prognosis [18, 29].

Several mechanisms may underlie the association between high UAER and BP progression. Abnormalities of glomerular endothelial cells and, perhaps, of glomerular basement membrane or podocytes could ultimately lead to increased filtration of albumin [30, 31]. Albuminuria is therefore regarded as a surrogate marker of not only glomerular but also systemic vascular damage, such as vascular endothelial dysfunction and abnormal vascular permeability [32]. Furthermore, reduction in the number of nephrons, via glomerular hyperfiltration in the residual nephrons followed by elevated intraglomerular pressure, glomerular injury and the concomitant incomplete absorption by proximal tubular cells, may also provide a link between higher albumin excretion and the development of hypertension [33, 34]. It is well established that as BP is tightly controlled by the kidney [35], renal dysfunction itself may be an underlying abnormality that leads to hypertension [36]. Altogether, we speculate that a decline in renal function could exaggerate the aforementioned mechanisms with regard to albumin excretion, and that this may explain the interaction observed in our analysis. Although further research is warranted to establish causality, albuminuria may reflect processes linked to both the pathogenesis of hypertension and renal dysfunction.

In our study design it is not directly possible to discern whether the results presented here are the results of specific comorbidities/conditions affecting the vascular wall or instead have a more universal meaning. In this sense we identified two conditions that may have influenced our findings: first, because diabetic nephropathy usually progresses with albuminuria, reduced eGFR and hypertension, diabetes was considered. However, diabetes status may not necessarily equal diabetic nephropathy, and although confirmation of our results in non-diabetics may suggest that this is not the case, we must acknowledge residual confounding. Second, association between UAER and blood pressure progression was also observed in individuals with UAER in the normal range. This |

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<th>Clinical Outcome</th>
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<td>A incidence of hypertension (n=71)</td>
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**FIGURE 1:** Odd ratios and 95% confidence intervals for hypertension incidence or the composite outcome of death and incident hypertension associated with UAER and stratified by the presence of reduced renal function. Multivariable logistic regression models showing associations of urinary albumin excretion rate (µg/min, logarithmically transformed with a square root) at baseline with (A) incidence of hypertension, defined as ABPM values indicating hypertension or intake of anti-hypertensive medication at re-examination (71 cases) in all available subjects (n=179) who did not present with hypertension or were on anti-hypertensive medication at baseline, and after stratification by kidney function strata; and (B) the composite outcome of incidence of hypertension or intake of anti-hypertensive medication at re-examination or death before re-examination (90 cases) in all available subjects (n=201; n=179 plus 22 individuals who died before re-examination and who did not have hypertension or were on anti-hypertensive medication at baseline), and after stratification by kidney function strata. Covariance in these models includes body mass index, smoking status, physical activity, cardiovascular disease, diabetes, hyperlipidaemia, estimated glomerular filtration rate, systolic blood pressure assessed by ambulatory blood pressure monitoring at baseline. OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.
is in line with previous studies reporting that the association between albuminuria and cardiovascular events is evident well below the current microalbuminuria threshold [28, 37–39]. Thus, our study adds to the bulk of evidence that challenge the designation of the entire range <20 μg/min as normoalbuminuria. Strengths of this study include the large, community-based sample, the prospective nature and longitudinal design. The use of ABPM at two visits 6 years apart, allowing us to study changes of BP on a continuous scale, is also an asset. Another strength of the study is that urinary albumin excretion was assessed in timed urine samples collected overnight rather than in a spot sample. We acknowledge, however, several limitations; while this cohort was extensively phenotype, residual confounding is a problem like in all observational studies. In this sense, because only those individuals surviving or motivated for their health may attend re-examination, potential survival bias needs to be acknowledged, and it justifies the use of composite outcome analysis considering death and hypertension incidence; we did not directly measure creatinine clearance rate but instead based our estimation of GFR on serum cystatin C concentrations. However, the serum cystatin C method has been validated with the gold standard method of iohexol clearance [15] and has been found to be superior to serum creatinine as a marker of kidney function [40]; the definition of CKD requires that eGFR is persistently decreased <60 mL/min/1.73 m² for at least 3 months while eGFR on serum cystatin C was measured at one time point [16]. UAER was measured only once while current recommendations suggest two consecutive measurements to diagnose micro- or macro-albuminuria [16]; however, potential misclassifications would result in an underestimation of the true risk reported here; Although the investigated cohort is relatively large and homogeneous, we may be limited in subgroup analyses and our results of CKD-segregated hypertension incidence specially need to be interpreted cautiously and confirmed in future studies. Finally, although the inclusion of elderly men with identical age and with similar geographical distribution reduced important confounding, few people had advanced kidney disease, and these results may not necessarily be extrapolated to women or other age categories.

CONCLUSIONS

Urinary albumin excretion in the community, even within the normal range, associated with a future increase of blood pressure as assessed by ABPM, and with the incidence of hypertension. The presence of concurrently impaired renal function modified and exacerbated these associations. Further interventional studies are warranted to evaluate the clinical relevance of our findings.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

This work was supported by the grants from the Swedish Research Council, the Center for Gender Medicine, the Swedish Heart-Lung foundation, as well as the Westman’s Foundation, all in Sweden. Baxter Novum is the result of a grant from Baxter Healthcare Corporation to Karolinska Institutet.

CONFLICT OF INTEREST STATEMENT

B.L. is affiliated with Baxter Healthcare Corporation. None of the other authors declare any conflict of interest.


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Received for publication: 24.1.2014; Accepted in revised form: 21.2.2014