Chapter 8

An elevated urinary albumin excretion predicts \textit{de novo} development of renal function impairment in the general population

Jacobien C. Verhave, Ron T. Gansevoort, Hans L. Hillege, Stephan J.L. Bakker, Dick de Zeeuw, Paul E. de Jong

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Abstract

Objectives
We questioned which factors determine the risk for developing renal function impairment.

Methods
To that purpose we studied the incidence of newly diagnosed impaired renal function (GFR < 60 mL/min/1.73 m²) in the PREVEND cohort (n= 8,592), which is enriched for the presence of albuminuria, and which was first studied in 1997/98.

Results
Of this cohort 6,894 subjects were studied again 4 years later. Subjects with known renal disease, GFR < 60 mL/min, missing GFR values or sediment abnormalities at the first screening were excluded from the present analysis (n= 872). We examined whether albuminuria is associated with the de novo development of an impaired renal function. GFR was 90.3 (SD 16.3) mL/min/1.73 m² at baseline and 11.6% of the subjects had an albuminuria of more than 30 mg/day. After a follow up of 4 years, 253 subjects (4.2%) were found to have a GFR < 60 mL/min/1.73 m². The subjects with newly diagnosed impaired GFR were older, had a higher blood pressure, serum cholesterol, plasma glucose and urinary albumin excretion at the first examination, and had a lower GFR to start with than those with a GFR > 60 at the second evaluation. Subjects with de novo impaired GFR had a comparable BMI and smoked less frequently compared to subjects with GFR > 60. In multivariate analysis urinary albumin excretion was independently predictive for the risk to develop an impaired GFR (p= 0.001).

Conclusions
In the general population measurement of urinary albumin excretion may prove to be a valuable tool to detect subjects at risk for later development of renal failure, independent of the presence of other cardiovascular risk factors.

Keywords
Renal function, Cockcroft-Gault, MDRD, urinary albumin excretion, PREVEND.
Introduction

Urinary albumin excretion (UAE) is a predictor of renal function impairment in diabetic subjects. Patients with type 1 diabetes frequently have an elevated glomerular filtration rate (GFR) the first decade after the diagnosis of the diabetes. In that period UAE gradually increases to the level of microalbuminuria (30-300 mg/24h). In subsequent years the risk for developing overt nephropathy and progressive renal failure is particularly high for those with microalbuminuria (1). This elevated UAE is not only a renal risk marker but also a cardiovascular risk marker in diabetes (2-4). In the general population albuminuria has also been proven to be of predictive value as marker for increased cardiovascular morbidity and mortality (5-7). However, longitudinal data on the predictive value of albuminuria for renal morbidity and mortality are thus far limited to diabetes. In the present study we therefore aimed to study the association of albuminuria at baseline and the de novo renal function impairment after four years follow-up in apparently healthy subjects.

Material and Methods

Study design and population

The PREVEND (Prevention of Renal and Vascular End-stage Disease) study was initiated in 1997 with the aim to investigate the impact of urinary albumin excretion on renal and cardiovascular disease in the general population (8). A cohort drawn from the city of Groningen, the Netherlands, (28-75 years) with an oversampling of subjects with an elevated urinary albumin concentration, was screened during two visits at the outpatient clinic. Pregnancy and insulin use were exclusion criteria. Overall 8,592 subjects were included. After a mean follow-up of 4.2 year (range 2.8-6.1) the participants were invited for identical visits to the outpatient clinic. Of the overall cohort 6,894 subjects were seen for the second screening. Subjects with known renal disease (n= 47), a GFR < 60 mL/min/1.73 m$^2$ (n= 336) or urinary sediment abnormalities (leukocytes > 75 /µl or erythrocytes > 50 erythrocytes /µl, or leukocytes = 75 and erythrocytes > 5 /µl) (n= 316) were excluded. In addition, 173 subjects were excluded because of missing data, leaving 6,022 subjects for the present analysis. Renal function was calculated by the Cockcroft-Gault formula (9) and by the MDRD formula (10). The Cockcroft-Gault formula was corrected for body surface area (BSA), the MDRD formula is per definition corrected for standard body surface area. Urinary albumin excretion is given as the mean of two 24 hour urine excretions. Impaired renal function was defined as GFR < 60 mL/min/1.73 m$^2$ (11).

At the initial visit serum creatinine was determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA) and during follow-up by photometric determination with the Jaffé method without deproteinisation (Merck KGaA, Darmstadt, Germany). To check whether this change in analytical method may influence results, serum samples were obtained of 200 subjects, known to have serum creatinine values evenly distributed over a range from 45 to 145 µmol/L. In these samples creatinine was measured simultaneously with both methods. Linear regression analysis was performed using the procedure proposed by Passing and Bablok (12,13). It appeared that serum creatinine measured by photometric determination was in general higher. To correct for this systematic bias a correction formula was introduced: Creatinine corrected = 1.027 X - 8.243, where X is serum creatinine measured by photometric determination.
**Statistical analyses**

Comparison of the population characteristics at baseline for normal versus impaired renal function at follow-up were tested for continuous variables by a Student t-test, for categorical variables by a Chi-square test and for UAE, because of its skewed distribution, by Kruskal-Wallis test. We used multivariate logistic regression to study the association of baseline UAE (corrected for confounders measured at baseline) and impaired GFR. The response variable of the logistic regression model was GFR < 60 mL/min/1.73 m$^2$. The predictor variables included in the regression model were UAE, gender, age, mean arterial pressure, BMI, plasma glucose, serum cholesterol, smoking, the use of antihypertensive, lipid lowering or antidiabetic medication, and renal function at baseline. For optimal goodness of fit, UAE and plasma glucose were transformed by a natural logarithm. A p-value of < 0.05 was considered significant. Repeated analyses were performed after exclusion of subjects with cardiovascular disease or diabetes at baseline. Analyses were also performed with GFR as calculated from the MDRD formula.

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**Figure 1.** Percentage of subjects with *de novo* renal function impairment for the categories of UAE at baseline.
Results

Mean age at the baseline investigations was 48 years (SD 12) and GFR was 90.3 (SD 16.3) mL/min/1.73 m², as measured by the Cockcroft-Gault formula. The cohort contained 51.5% men. Of the overall cohort, 696 (11.6%) subjects were newly diagnosed with an elevated UAE. Of these, 650 had microalbuminuria and 46 had macroalbuminuria (UAE > 300 mg/24h). After a follow up of 4 years 253 subjects (4.2%) had developed a GFR < 60 mL/min/1.73 m². Figure 1 shows an increasing prevalence of subjects with de novo renal impairment over the various categories of baseline UAE. Subjects who developed de novo renal impairment were older, had a lower GFR, higher blood pressure, plasma glucose, serum cholesterol and UAE at the first screening than those who did not develop renal impairment (table 1). More men had developed impaired renal function. Subjects with renal function impairment were less often smokers compared to subjects with a GFR > 60. No difference in BMI was observed.

Univariately, albuminuria was associated with de novo impaired renal function (table 2). After gender and age adjustment the association was still significant. In addition, after correction for the cardiovascular risk factors, albuminuria remained a predictor for renal function loss. The impact of baseline albuminuria to predict de novo renal function impairment is also shown in figure 2, which illustrates predicted odds ratio of a GFR < 60 according to UAE adjusted for the confounders in the multivariate model. Exclusion of the subjects with cardiovascular disease or diabetic patients did not influence the data significantly. Using MDRD estimated GFR instead of Cockcroft-Gault estimated GFR, hardly changed the results of the multivariate model.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>GFR second screening (mL/min/1.73 m²)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>≥60</td>
<td>&lt;60</td>
</tr>
<tr>
<td>N</td>
<td>5769</td>
<td>253</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>51.1</td>
<td>60.5</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>47 (11)</td>
<td>65 (7)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>91.1 (11.7)</td>
<td>100.9 (13.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.0 (4.1)</td>
<td>26.3 (3.5)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.6 (1.1)</td>
<td>6.0 (1.2)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.8 (1.1)</td>
<td>5.4 (1.9)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>37.1</td>
<td>26.5</td>
</tr>
<tr>
<td>UAE (mg/24h)</td>
<td>8.7 (6.1-14.7)</td>
<td>13.5 (7.1-30.2)</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>91.3 (15.8)</td>
<td>66.9 (6.5)</td>
</tr>
</tbody>
</table>

The mean ± standard deviation is given, except for UAE, which is expressed as median with the 25th and 75th percentiles.
Table 2. Albuminuria as predictor for GFR < 60 mL/min/1.73 m² after 4 year follow-up (Logistic regression model).

<table>
<thead>
<tr>
<th>Ln UAE</th>
<th>Unadjusted</th>
<th>Age and gender adjusted</th>
<th>Adjusted for confounders*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Ln UAE</td>
<td>1.63 1.46-1.82</td>
<td>1.31 1.15-1.49</td>
<td>1.30 1.11-1.52</td>
</tr>
</tbody>
</table>

* Baseline GFR, age, gender, mean arterial blood pressure, body mass index, serum cholesterol, plasma glucose, smoking, medication for hypertension, hypercholesterolaemia or diabetes.

Figure 2. Adjusted predicted odds ratio of GFR < 60 versus UAE of 2 mg/24h. The dashed lines indicate the 95% confidence interval. The gray area indicates the microalbuminuric range (UAE 30-300 mg/24h).
Discussion

We show that urinary albumin excretion is, also in the general population, predictive for the development of \emph{de novo} renal function impairment, independent of gender, age and cardiovascular risk factors. Renal impairment is common in the general population. However, it is usually asymptomatic and for that reason often not diagnosed. The Framingham Heart Study (data collection 1977-1983) showed that 8.9% of men and 8.0% of women have elevated serum creatinine levels (14). In the NHANES III (1988-1994) the prevalence of GFR $<$ 60 mL/min/1.73 m$^2$ was 4.7% (8.3 million subjects) (15), and in the baseline screening of our albuminuria enriched cohort 312 out of the 8592 (= 3.6%) subjects had a GFR below 60 mL/min/1.73 m$^2$. Early detection of renal impairment and subsequent institution of renoprotective treatment may lower the burden of ESRD and importantly, cardiovascular morbidity and mortality (16). In diabetes, the evidence that microalbuminuria predicts renal and cardiovascular complications resulted in diagnostic and therapeutic guidelines for clinical practice. These guidelines advise to screen patients with diabetes yearly for the presence of albuminuria (17). Therapeutical interventions that lower UAE delay the occurrence of renal complications in diabetes (18). In hypertensive patients, a comparable link between albuminuria and future renal and cardiac damage is highly likely (19-21), though screening for microalbuminuria in hypertension is not yet a routine in clinical practice. The present study shows that even in the general population UAE is predictive for \emph{de novo} renal function impairment. This finding might indicate that screening for albuminuria in the general population could lead to an early detection of progressive renal function impairment.

A recently published study of the Framingham Heart Study described predictors of kidney disease, as defined by sex-specific lowest five percent of MDRD estimated GFR (22). The authors conclude that \emph{de novo} renal impairment is predicted by baseline renal function, age and cardiovascular risk factors. Our data add that in the general population albuminuria seems to be a strong risk marker for the development of renal function impairment compared to the classical cardiovascular risk factors.

Serum creatinine during follow-up was corrected because a systematic error was detected that was introduced by a change in the analytical procedure. When this correction would not have been applied the number of subjects developing a GFR $<$ 60 mL/min/1.73 m$^2$ was 479 (8.0%). The results obtained however, would not be essentially different. Univariately and multivariately urinary albumin excretion would still predict \emph{de novo} renal function impairment significantly: Odds ratio of Ln UAE for predicting a GFR $<$ 60 mL/min/1.73 m$^2$ unadjusted 1.47 (1.34–1.61), adjusted for age and gender 1.15 (1.02–1.28) and adjusted for multiple confounders 1.25 (1.09–1.44). Our study is limited by the fact that the subjects included in the analyses are by definition subjects that survived for four years. It is generally accepted that both an increased UAE and diminished renal function are a risk factors or indicators for (cardiovascular) mortality. For this reason the presented results may be an underestimation. A second limitation is that we used a formula to estimate renal function instead of directly measuring renal function.

We conclude that albuminuria is a strong predictor of diminished renal function \emph{de novo}. The risk attributed to albuminuria is furthermore independent from cardiovascular risk factors. Albuminuria may therefore also in the general population prove to be a valuable risk marker for future renal function decline amenable for screening purpose.
References