Brief Report

Association between albuminuria and proteinuria in the general population: the AusDiab Study

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Abstract

Background. The relationship between urinary albumin and total protein excretion and the appropriateness of one test over the other are unclear due to the paucity of large epidemiological studies of albuminuria and proteinuria. In screening for renal and cardiovascular disease, whether to measure albuminuria, proteinuria or both, is currently an unanswered question.

Methods. Random urine samples from 10 596 (94.2%) participants of the Australian Diabetes, Obesity and Lifestyle Study were tested for albuminuria (urine albumin:creatinine \( \geq 30 \text{ mg/g} \)) and proteinuria (urine protein:creatinine \( \geq 0.20 \text{ mg/mg} \)). This study was a representative sample of the national non-institutionalized population drawn from 42 randomly selected urban and non-urban areas (census collector districts) across Australia.

Results. Among a representative cross-section of the Australian adult population, urine albumin excretion was strongly correlated with total protein excretion, particularly among the elderly, and those with diabetes mellitus, hypertension, obesity and renal impairment \( (P < 0.001) \). Albuminuria performed well as a screening test for proteinuria: sensitivity 91.7% [95% confidence interval (CI) 87.7–94.5%], specificity 95.3% [95% CI 94.9–95.7%] and negative predictive value 99.8% [95% CI 99.7–99.9%]. However, among those with proteinuria, 8% excreted albumin within the normal range.

Conclusions. While albuminuria may be a suitable test for general population screening for renal and cardiovascular disease, it should not replace testing for proteinuria in those with known or suspected renal disease.

Keywords: albuminuria; proteinuria; renal disease; screening

Introduction

Abnormal urinary protein excretion is a marker of renal disease and of increased renal and cardiovascular disease risk. Approximately 80 mg of protein per day is normally excreted in the urine, comprising filtered plasma proteins (albumin, immunoglobulin) and secreted protein (Tamm Horsfall) [1]. Urinary protein excretion may be quantified in terms of albumin or total protein. The relationship between urinary albumin and total protein excretion and the appropriateness of one test over the other are unclear due to the paucity of large epidemiological studies of albuminuria and proteinuria. A recent community-based study provided the opportunity to examine a large, randomly selected, population-representative cross-section of Australian adults and explore the relationship between urinary albumin (microalbuminuria and macroalbuminuria) and total protein excretion.

Subjects and methods

Random urine samples from Australians aged 25 years or over were tested for albuminuria (urine albumin:creatinine \( \geq 30 \text{ mg/g} \); microalbuminuria 30–299 mg/g and macroalbuminuria \( \geq 300 \text{ mg/g} \)) and proteinuria (urine protein:creatinine \( \geq 0.20 \text{ mg/mg} \), approximating an excretion of \( \geq 250 \text{ mg/day} \)) as part of the Australian Diabetes, Obesity and Lifestyle Study. Details of the survey methodology have been published elsewhere [2]. In brief, a representative sample of the national non-institutionalized population was drawn from 42 randomly selected urban and non-urban areas (census collector districts) across Australia, with six census collector districts in each of the six states and the Northern Territory. A total of 19214 households were
targeted, 17,129 were successfully contacted, and residents of 11,479 households agreed to a preliminary interview. All permanent residents 25 years of age or older of the households (n = 20,347) were invited to attend a 4-h screening programme at a local community hall. A total of 11,247 (55.3%) subjects provided written consent and completed the screening examination. Urine albumin:creatinine and protein:creatinine levels were available for 10,596 (94.2%) participants. Participants were representative of the Australian adult population, which is predominantly of European descent (90%), with a minority of participants of Asian (7%), Middle-Eastern (2%) or indigenous (1%) descent. Urine albumin was measured by rate nephelometry with the Beckman Array. The coefficient of variation was <3.1%. Urine protein was measured using pyrogallol red-molybdate with an Olympus AU600 auto-analyser. The coefficient of variation was <4.1%. Urine creatinine was measured by the modified kinetic Jaffe reaction using an Olympus AU600 auto-analyser. The coefficient of variation was <1.1%. All determinations were performed at a central laboratory (HITECH Pathology, Melbourne, Australia).

Statistical analyses were conducted using Stata version 6.0 (Stata Corporation, College Station, TX, 1999) survey commands for analysing complex survey data. All analyses were weighted to represent the non-institutionalized Australian population, thereby accounting for non-response and producing nationally representative estimates [2]. Covariates were summarized by albuminuria and proteinuria category. Differences between groups were tested by two-tailed unpaired t-test for continuous data and χ² test for categorical data. Evidence of effect modification by covariates: age (<60 vs ≥60 years), sex, diabetes mellitus status (no vs yes as defined by known diagnosis of diabetes mellitus on medication, fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose ≥11.1 mmol/l following a standard 75 g oral glucose tolerance test), hypertension status (<140/90 vs ≥140/90 mmHg or on blood pressure-lowering medication), body mass index (<30 vs ≥30 kg/m²) and Cockcroft–Gault estimated glomerular filtration rate (GFR; <60 vs ≥60 ml/min/1.73 m²) on the relationship between albuminuria and proteinuria was examined and considered to exist if the P-value for the interaction term was <0.10. Statistical significance was set at a P-value of <0.05 for all other analyses. Analyses involving correlations between albuminuria and proteinuria were performed after log transformation of the values due to non-normal distribution.

### Results

**Relationship between urinary albumin and total protein excretion**

Albuminuria was detected in 6.8% [95% confidence interval (CI) 5.5–8.1%] and proteinuria in 2.4% (95% CI 1.6–3.1%) of participants. Of those with proteinuria, 91% had albuminuria and 9% had an albumin:creatinine level within the normal range. Conversely, of those with albuminuria, 32% had proteinuria and 68% had a protein:creatinine level within the normal range. Table 1 shows the demographic and clinical characteristics of participants based on the presence or absence of albuminuria and proteinuria. Participants with proteinuria or albuminuria were older and had a higher prevalence of diabetes mellitus and hypertension compared with those with neither proteinuria or albuminuria, except for participants with proteinuria and no albuminuria who had a significantly lower prevalence of diabetes mellitus compared with all other participants, including those with neither proteinuria nor albuminuria, and for whom the prevalence of hypertension was not significantly different from other groups. The estimated GFR was significantly lower for participants with proteinuria or albuminuria compared with those with neither proteinuria nor albuminuria.

Albuminuria was correlated with proteinuria [β = 1.21 (95% CI 1.18–1.26) P < 0.001, R² = 72.1%]. Figure 1 demonstrates convergence toward the line of unity for the association between albuminuria and proteinuria with increasing degrees of proteinuria, suggesting the presence of an increased proportion of urine albumin at higher levels of total protein excretion. We explored this by stratifying participants by degree of proteinuria. Figure 2 demonstrates that the ratio urine albumin:total protein (mg/mg) increased with increasing degrees of proteinuria from 0.21 for those with protein excretion within the normal range, up to 0.73 for those with moderate to heavy proteinuria (urine protein:creatinine > 0.80, approximating > 1 g/day; P < 0.001 vs normal). The correlation between albuminuria and proteinuria was significantly greater in participants: ≥60 years compared with <60 years.

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**Table 1. Clinical characteristics by albuminuria and proteinuria category**

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>No proteinuria</th>
<th>Micro-</th>
<th>Macro-</th>
<th>Proteinuria</th>
<th>No proteinuria</th>
<th>Micro-</th>
<th>Macro-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, %</td>
<td>93.0 (0.6)</td>
<td>4.6 (0.4)</td>
<td>0.0</td>
<td>0.2 (0.1)</td>
<td>1.5 (0.2)</td>
<td>0.7 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>47.5 (0.7)†</td>
<td>59.8 (1.8)*</td>
<td>4-h</td>
<td>58.1 (4.0)*</td>
<td>63.9 (2.1)*</td>
<td>61.0 (2.6)*</td>
<td></td>
</tr>
<tr>
<td>Sex, % men</td>
<td>50.1 (0.6)</td>
<td>42.3 (2.2)*</td>
<td>–</td>
<td>51.5 (12.7)</td>
<td>42.9 (4.7)</td>
<td>52.1 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>6.3 (0.7)†</td>
<td>25.2 (3.9)*</td>
<td>4-h</td>
<td>0.9 (0.9)*</td>
<td>28.2 (3.8)**</td>
<td>35.4 (7.4)**</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>26.5 (1.7)</td>
<td>62.4 (4.2)*</td>
<td>–</td>
<td>43.2 (14.9)</td>
<td>67.5 (4.6)*</td>
<td>76.3 (9.2)**</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 (0.2)</td>
<td>27.4 (0.4)</td>
<td>–</td>
<td>26.4 (1.3)</td>
<td>27.7 (0.6)</td>
<td>27.6 (1.0)</td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min/1.73 m²</td>
<td>86.5 (0.8)†</td>
<td>73.9 (2.9)*</td>
<td>–</td>
<td>73.1 (4.9)*</td>
<td>69.8 (4.2)*</td>
<td>67.2 (3.4)*</td>
<td></td>
</tr>
</tbody>
</table>

Mean or prevalence (standard error).

*P < 0.05 for no proteinuria and no albuminuria compared with all other categories; †P < 0.05 for proteinuria and no albuminuria compared with all other categories.
\[ \beta = 1.31 \text{ (95\% CI 1.26--1.35)} \quad R^2 = 81.2\% \text{ vs } \beta = 1.12 \text{ (95\% CI 1.05--1.18)} \quad R^2 = 61.5\% \text{, respectively, } P < 0.001 \text{ for interaction}, \]

with diabetes mellitus compared with without \[ \beta = 1.34 \text{ (95\% CI 1.30--1.37)} \quad R^2 = 85.6\% \text{ vs } \beta = 1.18 \text{ (95\% CI 1.13--1.23)} \quad R^2 = 68.9\% \text{, respectively, } P < 0.001 \text{ for interaction}, \]

with hypertension compared with without \[ \beta = 1.31 \text{ (95\% CI 1.28--1.34)} \quad R^2 = 81.9\% \text{ vs } \beta = 1.07 \text{ (95\% CI 1.01--1.14)} \quad R^2 = 59.1\% \text{, respectively, } P < 0.001 \text{ for interaction}, \]

with body mass index \( \geq 30 \text{ kg/m}^2 \) compared with <30 kg/m\(^2\) \[ \beta = 1.29 \text{ (95\% CI 1.24--1.35)} \quad R^2 = 78.7\% \text{ vs } \beta = 1.20 \text{ (95\% CI 1.15--1.24)} \quad R^2 = 70.7\% \text{, respectively, } P = 0.001 \text{ for interaction} \]

and with estimated GFR <60 ml/min/1.73 m\(^2\) compared with \( \geq 60 \text{ ml/min/1.73 m}^2 \) \[ \beta = 1.29 \text{ (95\% CI 1.25--1.34)} \quad R^2 = 82.9\% \text{ vs } \beta = 1.18 \text{ (95\% CI 1.13--1.24)} \]

[\( R^2 = 67.1\% \), respectively, \( P = 0.001 \text{ for interaction} \).]

The correlation between albuminuria and proteinuria was however similar for men and women \[ \beta = 1.22 \text{ (95\% CI 1.16--1.28)} \quad R^2 = 71.6\% \text{ vs } \beta = 1.20 \text{ (95\% CI 1.15--1.24)} \quad R^2 = 72.9\% \text{, respectively, } P = 0.483 \].

Sensitivity of albuminuria as a test for proteinuria

Table 2 demonstrates that testing for albuminuria identified subjects with proteinuria with a sensitivity of 91.7\% (95\% CI 87.7--94.5\%) and specificity of 95.3\% (95\% CI 94.9--95.7\%). In this cross-section of the general population, the negative predictive value was 99.8\% (95\% CI 99.7--99.9\%) and positive predictive value 32.4\% (95\% CI 29.0--35.8\%).
Table 2. Performance characteristics of albuminuria as a test for proteinuria among the general Australian adult population (n = 10 596)

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>2.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Negative</td>
<td>6.8%</td>
<td>93.2%</td>
</tr>
</tbody>
</table>

Albuminuria = urine albumin:creatinine ratio ≥ 0.20 mg/mg; proteinuria = protein:creatinine ratio ≥ 30 mg/g; proteinuria = protein:creatinine ratio ≥ 1.0 mg/mg. Sensitivity 91.7% (95% CI 87.7–94.5%) and specificity 95.3% (95% CI 94.9–95.7%). Positive predictive value 32.4% (95% CI 29.0–35.8%) and negative predictive value 99.8% (95% CI 94.9–95.7%).

Discussion

Measurement of urinary protein excretion is common to many areas of medicine, and provides information on diagnosis, prognosis and risk stratification for people with renal disease, diabetes mellitus and cardiovascular disease. Nevertheless, there is a lack of consensus on whether to measure urine albumin, total protein or both in many clinical situations. This study provides the first large-scale, population-based analysis of the relationship between urinary albumin and total protein.

In the Australian adult population, urinary albumin excretion was tightly correlated with total protein excretion. However, several important discrepancies between albuminuria and proteinuria were evident. First, albuminuria was more prevalent than proteinuria, largely reflecting the lower threshold for the detection of microalbuminuria. Secondly, 8% of participants with proteinuria, or 0.2% of the general population, were found to have a urinary albumin excretion within the normal range. This group of participants with proteinuria in the absence of albuminuria were less likely to have diabetes mellitus and there was a trend for hypertension to be less prevalent when compared with those with proteinuria in the presence of albuminuria. Thirdly, albumin was not excreted as a constant proportion of total protein, and the ratio of albumin to total protein was 2- to 3-fold higher for those with significant proteinuria compared with those with normal protein excretion. The correlation between urinary albumin and total protein was significantly greater for the elderly and for participants with hypertension, diabetes mellitus, obesity or renal impairment. These findings provide important insights in relation to the implications of population and targeted screening for proteinuria.

Among people with diabetes mellitus [3], hypertension [4] or advanced age [5], microalbuminuria is a validated marker of cardiovascular risk and overall mortality. In this population-based study, albuminuria performed well as a screening test for proteinuria. Albuminuria identified 91.7% of those with proteinuria and provided an excellent negative predictive value in the general community setting (99.8%). On the other hand, testing for proteinuria identified less than one-third of all cases of albuminuria. Thus, testing for albuminuria appears to be a useful measure of urinary protein excretion in a community context. However, the implications of which test to use differ for patients with known or suspected renal disease. Among this subgroup of the population, proteinuria is an important guide to diagnosis, prognosis and patient management [6]. Our study found that 8% of those with proteinuria tested negative for albuminuria. Albumin-poor proteinuria may be seen in cases of paraproteinaemia or interstitial nephropathies, where proteinuria may be the major marker of kidney disease [1]. In such cases, the diagnosis may be missed if albuminuria is tested for instead of proteinuria.

Comparison of the prevalence of albuminuria and proteinuria in this study with that of other population-based studies is difficult due to differences in the time period over which studies were undertaken, the demographic and clinical characteristics of participants in the studies, the type of urine specimens tested, the tests performed to measure and the thresholds used to define albuminuria and proteinuria. Other population-based studies published to date reporting albuminuria or proteinuria have been undertaken over the last five decades, and all prior to 1995 [7–18]. This compares with more contemporary data from this study, reflecting more current trends in the prevalence and management of important risk factors such as hypertension and diabetes mellitus. Albuminuria and proteinuria have been measured in single untreated random urine specimens [9–13,15,17,18] as in this study, but also in first voided urine specimens [14,16]. Albuminuria and proteinuria most commonly have been measured semi-quantitatively by dipstick [7–11,15] but have also been quantitated either as albumin concentrations [12–14,16] or as a ratio with urine creatinine [17,18], as was performed in this study for both albumin and protein.

This epidemiological study supports testing for albuminuria rather than proteinuria as an indicator of renal, cardiovascular and mortality risk among the general population. However, among those with known or suspected renal disease, measurement of total protein excretion may provide superior diagnostic and prognostic information. This study provides important information for the development of an evidence base from which guidelines on the implications of, urinary albumin and protein excretion in a general population setting can be formulated.

Acknowledgements. We wish to thank the participants, Survey Team and Steering Committee of the AusDiab Study. The AusDiab Study was supported by the Commonwealth Department of Health and Aged Care, State Governments of Queensland, South Australia, Tasmania, Western Australia and Victoria, and Territory Health Services, the Australian Kidney Foundation, Diabetes Australia (Northern Territory), the International Diabetes...
Institute, Eli Lilly (Australia), Janssen-Cilag (Australia), Knoll Australia, Merck Lifha s.a. Alphapharm, Merck Sharp & Dohme (Australia), Pharmacia and Upjohn, Roche Diagnostics, Servier Laboratories (Australia), SmithKline Beecham International, BioRad Laboratories, HITECH Pathology and Qantas Airways.

Conflict of interest statement. None declared.

References


Received for publication: 18.12.02
Accepted in revised form: 25.4.03