The natural history of renal disease in Australian Aborigines. Part 1. Changes in albuminuria and glomerular filtration rate over time

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Background. The purpose of this study was to describe changes over time in albuminuria and glomerular filtration rate (GFR) in a cohort of Australian Aborigines from a community with high rates of renal disease and renal failure.

Methods. Participants were 486 adult community members (20+ years at first exam) who were screened for renal disease and related factors on at least two occasions (mean 2.7 occasions), at least a year apart, between 1990 and 1997. Renal function was assessed by the albumin:creatinine ratio (ACR; g/mol) on a random urine specimen and by the GFR estimated from the Cockcroft-Gault formula. Evolution over time was expressed as the average annual changes in these parameters.

Results. On baseline examination, 70% of participants had albuminuria (ACR 1.1+ g/mol) with a significant net increase in ACR and a fall in GFR in the cohort over time. Among individuals, however, changes were strongly correlated with ACR levels at baseline. There was no loss of GFR in persons with normal renal parameters at baseline and a rapid loss of GFR in those with substantial levels of albuminuria at baseline. Other factors significantly correlated with progression of ACR included age, baseline body mass index and systolic blood pressure, the presence of diabetes (or levels of fasting glucose), and elevated levels of serum gamma glutamyl transferase. Factors significantly associated with loss of GFR included body mass index, diabetes, systolic and diastolic blood pressures, microscopic hematuria, and marginally high cholesterol levels.

Conclusion. Albuminuria progresses and GFR is lost over time in individuals in this community, at rates that are strongly dependent on levels of pre-existing albuminuria. Much loss of GFR and all renal failure should be avoided by preventing the development of albuminuria and minimizing its progression. This depends on improving the weight, blood pressure, and metabolic profile of the entire community and reducing infections. Modification of the course in people with established disease depends on vigorous control of blood pressure and the metabolic profile and the specific use of angiotensin-converting enzyme inhibitors.

Aborigines in the remote areas of Australia are experiencing an epidemic of renal disease and renal failure [1, 2]. Albuminuria is common, and renal biopsies, while including all of the usual pathologies, are remarkable for the high proportion with distinctly enlarged glomeruli and variable degrees of sclerosis (abstract; Howard et al, Aust NZ Soc Nephrol 1996) [3, 4]. We have already described a community-based study in one high-risk group, with a recent end-stage renal disease incidence of 2700 per million [5–7]. Albuminuria was pervasive, and (on cross-sectional study) increased with increasing age. The level of albuminuria was also significantly correlated with body mass index (BMI), blood pressure, glucose and lipid levels, heavy drinking, the presence of scabies, a history of poststreptococcal glomerulonephritis, the presence of hematuria, and inversely with birth weight. Average GFR values were slightly higher in persons with subtle levels of pathologic albuminuria than in those with normal albumin excretion and then, beginning in the midmicroalbuminuria range, were progressively lower as levels of albuminuria increased further [8].

The increase in ACR and serum creatinine with increasing age on this cross-sectional view could represent progression in individuals over time and/or a cohort phenomenon. These have different implications for future disease rates. The current report describes the longitudinal evolution of ACR and GFR in adults in this community and their determinants. We have already described the implications of albuminuria and GFR for renal failure and natural death [9], and further develop that theme in an accompanying article in this issue [10].

Key words: kidney failure in Aborigines, end-stage renal disease, progressive renal disease, death and GFR, albuminuria, epidemic of kidney disease, hypertension, obesity, metabolic profile.

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METHODS

All members of this remote Aboriginal community were invited to participate in a renal disease screening program conducted between 1990 and 1997. The study cohort consisted of people who were age 20+ years at their first examination and were screened on at least two separate occasions at least one year apart, with a full set of observations on each occasion, before the institution of systematic antihypertensive/renal protective treatment, death, dialysis, or the close-out of the study in April 1998.

Height, weight, and blood pressure were measured, and skin was examined for sores and scabies. The urinary albumin:creatinine ratio (ACR g/mol) was measured on a random urine specimen using the Beckman radioimmunoassay for albumin determinations. The following categories of ACR were employed for the analyses: ACR <1.1 = normal; ACR 1.1 to 3.3 = suspicious; ACR 3.4 to 33 = microalbuminuria; and ACR 34+ = overt albuminuria [5]. People with overt albuminuria were further subdivided into those with ACR 34 to 99, ACR 100 to 199, and ACR 200+. Serum creatinine was measured, and glomerular filtration rate (GFR) was estimated by the Cockcroft-Gault formula [11]. Persons were considered to be diabetic if this diagnosis already existed or if a random blood glucose or a two-hour postglucose challenge blood glucose level exceeded 11 mmol/L [12]. Fasting glucose levels were measured in 249 of the 486 people on the first examination. Levels of cholesterol and serum gamma glutamyl transferase (GGT) were also measured.

In persons who had only two visits (N = 195), the average annual change in ACR (GFR) was calculated as follows: ΔACR = (last ACR – first ACR)/time between first and second visits. For people who had more than two visits, single linear regression coefficients were used to estimate the average annual change in ACR and GFR [13]. The association of continuous variables with change in ACR (not normally distributed) was evaluated by nonparametric Spearman analysis, and correlations with changes in GFR, which were normally distributed, were analyzed by linear regression. The associations of dichotomous variables with changes in ACR and GFR were evaluated by two-tailed t tests. All analyses were performed using Stata Statistical software [14].

RESULTS

Four hundred eighty-six people qualified for inclusion. They were followed for 1 to 6 years, with a mean of 3.9 years. They underwent a mean of 2.7 examinations at least a year apart; 195 people had two examinations, and 291 had three or more examinations. These people represent 63% of adults who were screened at least once in the program with a full set of observations (N = 776) and approximately 57% of the entire adult community (N = 850).

Table 1 summarizes the characteristics of participants at baseline exam; 268 were male and 218 were female. Their age at first exam ranged from 20 to 76 years (mean 34.3 years). Fifty-one (10.5%) were diabetic at time of baseline exam.

Table 2 summarizes the renal status of participants at baseline examination. Albuminuria was common, with a group mean well above the upper limit of normal of 1.0 g/mol. Only 29.8% of persons had normal ACRs, while 31.5% had microalbuminuria and 21.6% had overt albuminuria. Average serum creatinine was “normal,” but there was a wide variation. Average GFR was less than 100 mL/min/1.73 m². Nineteen percent of people had microscopic hematuria. All these findings were similar to those of people who were not included in the longitudinal cohort [6].

Figure 1 shows the correlation between estimated GFR and ACR values at baseline. It hints at higher GFRs in people with subtle levels of pathologic albuminuria and shows progressively lower GFRs in people with increasing intensity of pathologic albuminuria thereafter.

Table 3 shows the average annualized changes in clinical parameters over time in the entire group. There were significant net increases in weight, body mass index (BMI), and blood pressure, as well as ACR and serum creatinine, and GFR decreased significantly.
Table 3. Average annual change in clinical characteristics in 486 participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Annual change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight kg</td>
<td>+0.52 (1.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>+0.22 (.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>+0.96 (7.0)</td>
<td>0.0026</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>+0.51 (4.8)</td>
<td>0.0195</td>
</tr>
<tr>
<td>ACR g/mol, mean</td>
<td>+4.46 (22.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>g mean</td>
<td>+1.10 (1.46)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine μmol/L</td>
<td>+3.02 (20.2)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Estimated GFR mL/min</td>
<td>−1.14 (4.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estimated GFR mL/min/1.73 m²</td>
<td>−1.41 (5.75)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations are: BMI, body mass index; ACR, albumin:creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.

Changes in ACR and GFR were quite variable. Figures 2 and 3 demonstrate their relationship with baseline ACR on a continuum. There was little change in ACR in people with normal ACR values at baseline and there was increasing annual net change in ACR, both positive and negative, with increasing levels of pathologic albuminuria at baseline. There were wide variations in change of GFR at all levels of baseline ACR, but the line of best fit suggests that, on average, GFR was stable or increased slightly in people with subtle levels of albuminuria and then began to fall in people with increasing levels of pathologic albuminuria, starting in the early to midmicroalbuminuria range; this fall became quite dramatic at higher levels of overt albuminuria at baseline.

Figure 4 summarizes the net changes in ACR and GFR changes by category of baseline ACR. The average annual change in ACR was very small and varied little in people with normal ACR values at baseline; it was positive in people with pathologic albuminuria at baseline, increasing as the level of baseline albuminuria rose, and then appeared to fall at extreme baseline levels of overt albuminuria. There was an apparent net increase in GFR among people with normal and suspicious levels of ACR at baseline. Then there was a consistent decrease in GFR with increasing levels of pathologic levels of albuminuria at baseline; this was already clear in persons with microalbuminuria, who on average were losing an average of 2.2 mL/min/year of GFR, and culminated in an average loss of 11.6 mL/min/year in those with ACR 200+ at first observation. Average annual changes in serum creatinine, which do not reflect interim changes in weight and age, confirmed these trends.
Table 4. Factors at baseline correlating with annual changes in albumin:creatinine ratio (ACR) (g/mol)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient, P</th>
<th>Coefficient, P adjusted for baseline ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>0.18, &lt;0.001</td>
<td>0.18, 0.001</td>
</tr>
<tr>
<td>ACR g/mol</td>
<td>0.18, &lt;0.001</td>
<td>0.18, 0.001</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>0.23, &lt;0.001</td>
<td>0.23, 0.001</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>0.11, =0.01</td>
<td>0.11, =0.01</td>
</tr>
<tr>
<td>Fasting glucose mmol/L⁺</td>
<td>0.16, =0.012</td>
<td>0.16, =0.012</td>
</tr>
<tr>
<td>Diabetes y/n</td>
<td>6.75, &lt;0.001</td>
<td>6.75, &lt;0.001</td>
</tr>
<tr>
<td>High GGT y/n</td>
<td>2.63, =0.03</td>
<td>2.63, =0.03</td>
</tr>
</tbody>
</table>

Abbreviations are: BMI, body mass index; SBP, systolic blood pressure; GGT, gamma glutamyl transferase.

* Fasting glucose measured on only 249 of the 486 people

Table 5. Factors at baseline correlating with annual changes in glomerular filtration rate (GFR) (mL/min/1.73 m²)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient, P</th>
<th>Coefficient, P adjusted for baseline ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR g/mol</td>
<td>-0.30, &lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>-0.22, &lt;0.001</td>
<td>-0.13, =0.009</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>-0.05, &lt;0.001</td>
<td>-0.018, =0.19</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>-0.07, =0.001</td>
<td>-0.017, =0.39</td>
</tr>
<tr>
<td>Fasting glucose mmol/L⁺</td>
<td>-0.46, =0.003</td>
<td>-0.20, =0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-3.35, &lt;0.001</td>
<td>-1.08, =0.21</td>
</tr>
<tr>
<td>Hematuria</td>
<td>-1.96, =0.003</td>
<td>-0.93, =0.14</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>-1.25, =0.06</td>
<td>-0.64, =0.92</td>
</tr>
<tr>
<td>Female</td>
<td>-0.89, =0.09</td>
<td>-0.81, =0.10</td>
</tr>
</tbody>
</table>

Abbreviations are: ACR, albumin:creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

* Fasting glucose measured on only 249 of the 486 people

There were no consistent correlations between annual changes in ACR or GFR themselves.

Table 4 shows factors that on univariate analysis were significantly correlated with increase in ACR. In nonparametric analysis, continuous variables that were significantly correlated with increase in ACR included baseline ACR, age, BMI, systolic blood pressure (SBP), fasting glucose levels, diabetes, and high GGT levels. The apparently facilitating effect of female sex (coefficient 1.96, P = 0.14) and diastolic blood pressure (DBP; coefficient = 0.07, P = 0.15) did not reach significance, and elevated cholesterol levels (P = 0.34) and hematuria (P = 0.31) were not significant determinants.

The distribution of changes in ACR could not be normalized, so multivariate models could not be derived.

Table 5 shows factors that correlated significantly with a loss of GFR in univariate analysis. These included baseline ACR, BMI, SBP, DBP, fasting glucose, diabetes, the presence of hematuria, and marginally, high cholesterol levels. Females tended to have higher rates of loss of GFR, but the association was not significant.

In multivariate analysis, factors that were significant (P < 0.10) in the final model of change in GFR included baseline ACR, age, SBP, female sex, and BMI; thus:

\[ \Delta GFR = 5.53 - 0.848 \ln \text{ACR} (\text{CI} -1.13, -0.56, P < 0.001) \]

- 0.059 age (CI 0.012, 0.106, P < 0.014)
- 0.034 SBP (CI −0.064, −0.003, P < 0.033)
- 1.001 female sex (CI −2.06, −0.06, P = 0.064)
- 0.087 BMI (CI −0.188, 0.14, P = 0.094)

In most models, >75% of the explained variance in \( \Delta \text{GFR} \) was carried by baseline ACR.

**DISCUSSION**

Renal disease progressed over time in adults in this community. There was a net progression of albuminuria and loss of GFR over time, although individual changes...
varied. There was little change in albuminuria in people with normal levels at baseline, a net increase in those with mild and moderate pre-existing albuminuria, and a net fall in those with heavy pre-existing levels, which probably reflects the loss of filtering surface as disease progresses. Loss of GFR was critically dependent on pre-existing levels of albuminuria. There was no measurable loss over a year in persons without pathologic albuminuria at baseline, a significant loss in people with microalbuminuria at baseline (mean 2.1 mL/min/year), and an average loss of GFR of almost 12 mL/min/year in people with ACR 200+ at baseline. Thus, levels of albuminuria predict loss of renal function. As we describe elsewhere [9, 10], they also powerfully predict renal failure, as well as natural death.

Other factors correlated with progression of albuminuria and/or loss of GFR include female sex, age, BMI, diabetes, or increasing blood glucose, blood pressure, microscopic hematuria, high GGT levels, and perhaps cholesterol levels. These factors also correlate with intensity of albuminuria on cross-sectional study of this population [6] and indicate target areas for interventions. The correlation of increasing BMI with increasing ACR and loss of GFR emphasizes the important effect of adult weight on renal disease [5, 6, 15]. The predictive value of persons with ACR >1.1 g/mol and the fact that mean GFR is highest in people with early to midrange microalbuminuria on the cross-sectional data might be hinting at hyperperfusion/hyperfiltration early in the disease course. This process, well recognized in early diabetic nephropathy [32], might thus be generalizable to the broader spectrum of renal disease and provide a point for intervention at a much earlier stage [25, 29].

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