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). There was 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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glucose levels were measured in 249 of the 486 people than 100 mL/min/1.73 m$^2$. Nineteen percent of people blood glucose level exceeded 11 mmol/L [12]. Fasting but there was a wide variation. Average GFR was less to be diabetic if this diagnosis already existed or if a ran- while 31.5% had microalbuminuria and 21.6% had overt

Cockcroft-Gault formula [11]. Persons were considered 1.0 g/mol. Only 29.8% of persons had normal ACRs,

and ACR 200

ries of ACR were employed for the analyses: ACR

assay for albumin determinations. The following catego-

min:creatinine ratio (ACR g/mol) was measured on a and approximately 57% of the entire adult community

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 treat-

ment, 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 radioimmuno-

assay for albumin determinations. The following catego-

cies 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

glomerular filtration rate (GFR) was estimated by the a group mean well above the upper limit of normal of

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 m$^2$. 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.
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></td>
</tr>
<tr>
<td>ACR g/mol</td>
<td>0.18, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>0.23, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>0.11, &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose mmol/L*</td>
<td>0.16, =0.012</td>
<td></td>
</tr>
<tr>
<td>Diabetes y/n</td>
<td>6.75, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>High GGT y/n</td>
<td>2.63, =0.03</td>
<td></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.

Fig. 4. Annual changes in albumin:creatinine ratio (ACR) (A) and average annual changes in glomerular filtration rate (GFR) (B) by baseline ACR category. Data are mean ± SE.

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 hematuria for progression might reflect an inflammatory element in the primary process, possibly related to skin infections and poststreptococcal glomerulonephritis [6]. It might also reflect structural damage associated with advancing disease.

Several reports describe the predictive value of albuminuria (proteinuria) for loss of GFR in people with obvious renal disease, usually studied in nephrology practices [16–22]. We describe this relationship at a community level, in people representing the community's practices [16–22]. We describe this relationship at a community level, in people representing the community's practices [16–22].

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REFERENCES


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While our results illuminate the relationship between pathologic albuminuria and loss of GFR, they might also be exposing different events early in the evolution of renal disease. The increase in mean GFR over time in 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].
14. StataCorp: Stata Statistical Software (release 60). College Station, Stata Corporation, 1999