Chronic kidney disease (CKD) is one component of a spectrum of chronic disease in Aboriginal Australians. CKD is marked by albuminuria, which predicts renal failure and nonrenal natural death. Rates vary greatly by community and region and are much higher in remote areas. This reflects the heterogeneous characteristics and circumstances of Aboriginal people. CKD is multideterminant, and early-life influences (notably low birth weight), infections (including poststreptococcal glomerulonephritis), metabolic/hemodynamic parameters, and epigenetic/genetic factors probably contribute. CKD is associated intimately with cardiovascular risk. Albuminuria progresses over time, with a high incidence of new onset of pathologic levels of albuminuria in all age groups. All the usual morphologic findings are found in renal biopsy specimens. However, glomerular enlargement is notable in individuals from remote regions, but not those living closer to population centers. Glomerulomegaly probably represents compensatory hypertrophy caused by low nephron number, which probably underlies the accentuated susceptibility to renal disease. In the last decade, health care services have been transformed to accommodate systematic chronic disease surveillance and management. After a relentless increase for 3 decades, rates of Aboriginal people starting renal replacement therapy, as well as chronic disease deaths, appear to be stabilizing in some regions. Official endorsement of these system changes, plus ongoing reductions in the incidence of low birth weight and infections, hold promise for continued better outcomes.

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amalgamation of several different tribal groups. Very few are truly nomadic today. They are in epidemiologic transition, marginalized and poor, with substandard living conditions, poor education, few employment opportunities, and inadequate services of all types. Their health profile reflects lingering “Third World” conditions as well as lifestyle diseases considered part of westernization. Standardized adult mortality rates are 3-8 times those of non-Aboriginal Australians, with cardiovascular disease the leading cause, and renal failure rates are very high.

Aboriginal people who live less remotely are very heterogeneous. The largest numbers live around population centers in New South Wales and Queensland. In general, they have had longer exposure to Western influences and have a more non-Aboriginal genetic admixture. Although they have many unmet needs, their mortality and renal failure rates are significantly lower than those of remote Aboriginal people.

This review addresses chronic kidney disease (CKD), a component of the chronic disease spectrum (cardiovascular disease, type 2 diabetes, hypertension, and CKD), which has appeared in Aboriginal people since the early 1980s.

END-STAGE RENAL DISEASE AND RENAL REPLACEMENT THERAPY

Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) data show that the incidence nationwide of Aborigines with end-stage renal disease (ESRD) resulting in renal replacement therapy (RRT), with age adjustment, is about 10 times that of non-Aboriginal Australians. Patients with ESRD are younger than their non-Aboriginal counterparts, there is overall a female predominance, and they have high rates of comorbid conditions. However, there is vast variation by region among Aboriginal people across Australia, as shown further by Cass et al from 1993 to 1998, and confirmed 10 years later by Preston-Thomas et al. In some remote regions in the Northern Territory, the incidence of RRT in Aboriginal people is more than 20-fold that of non-Aboriginal Australians, whereas rates in Aboriginal people in major metropolitan centers are scarcely higher than those of non-Aboriginal Australians. In relation to today’s state and territory jurisdictions, rates are highest where a greater proportion of Aboriginal people live remotely (Northern Territory...
and Western Australia) and lowest where most indigenous people live in and around cities, such as New South Wales and Queensland (Fig 2). Regional rates also correlate strongly with socioeconomic disadvantage, assessed by using indices of house crowding, low birth weight, poor educational attainment, low employment, and low income.\textsuperscript{9,10} Regional mortality follows a similar pattern.\textsuperscript{4,5} The proportion of Aborigines with terminal renal failure who do not receive RRT is under study.

In the last 10 years, dialysis units have been constructed in many remote locations. However, many Aboriginal people still need to relocate or travel long distances to access RRT. Relocation poses serious housing, social, and emotional difficulties that compound the alienation and disempowerment attendant on dependence on a highly medicalized technical form of life support away from family and community supports. Their median survival on dialysis therapy is short, they are less likely to be referred for or receive a kidney transplant, and they have lower transplant and patient survival.\textsuperscript{7,11,12} Furthermore, many Aboriginal living transplant donors later develop renal insufficiency.\textsuperscript{13} This is compatible with high background rates of CKD in some regions, the relentless increase in clinical manifestations with increasing age (discussed later), and family clustering of CKD. Standard donor evaluation currently is inadequate to identify such susceptibility to renal disease. Living donation should be applied cautiously until these matters are understood better.

The costs of RRT for indigenous people and treatment of their intercurrent complications and comorbid conditions are very high.\textsuperscript{14} That expenditure competes with primary health care for resources within a finite health care budget that already is strained by the extra costs of health care delivery in remote areas. The relative responsibilities of states/territories versus federal government for funding primary care, specialist services, hospitalizations, and RRT increasingly are debated.\textsuperscript{15}

Until recently, the incidence of treated RRT in indigenous people had been increasing relentlessly. However, higher numbers of people developing ESRD mean higher costs because of hospitalizations and RRT, but they do not always mean worsening population health status. Decreases in competing mortality, such as deaths in low-birthweight infants and children and all-cause deaths in adults, create a larger pool of patients at risk by increasing longevity. The well-recognized decreases in infectious deaths are one consideration, but improved management of diabetes and cardiovascular disease also is extending adult life, potentially allowing progression of coexisting nephropathy to end stage. That said, numbers and rates of people starting RRT in some remote regions seem to have leveled off in the last few years (Fig 2). There also seems to be a decrease in all-cause deaths and chronic disease deaths generally.\textsuperscript{5,16-19}

**EPIDEMIOLOGIC STUDIES**

Reports of renal and related chronic diseases in indigenous people in Australia are increasing. Discrete research studies are being supplemented by surveillance data from health services. A unified approach to chronic disease surveillance nationwide and ongoing evaluation through well-resourced information systems ultimately should eliminate the need for surveys, unless community participation is deficient and/or special testing is required. Introduction of a unique health care number for each Australian ultimately will permit linking of profiles and episodes of

![Figure 2](image-url)
service use to individuals and linkage of service use of individuals across the health care continuum.

In all regions, rates of hypertension, renal disease, and type 2 diabetes in indigenous people are high, but vary by region and community. Rates increase with age, and hypertension and proteinuria appear much earlier in the life course and at higher rates than type 2 diabetes, as shown in Fig 3.20-23 Figure 4 shows the extent of risk exacerbation in 3 remote communities in one region of the remote Northern Territory relative to those in the contemporaneous AusDiab (Australian Diabetes, Obesity and Lifestyle) study, which was conducted in largely nonindigenous Australians.24 Reasons for differences in rates are poorly understood, although various communities are composed of different mixes of tribal groups in different stages of epidemiologic and health transition and have different types of body habitus.

Much has been learned from detailed studies in 2 remote communities in the Top End of the Northern Territory that are >700 km apart.25-29 Both used albumin-creatinine ratio (ACR; grams per mole) on a random urine specimen as the primary renal disease marker. ACR proved to be very robust; it was stable under various conditions of diuresis and glucose loading, albumin levels were stable up to 10 years of storage at −80°C,30 and albumin levels assayed using both immunonephelometry and high-performance liquid chromatography had identical cross-sectional correlations with clinical profiles and identical predictive values for terminal outcomes when examined along the continuum of their own values.31 Furthermore, urine protein excretion using dipstick correlated fairly well with ACR, with more than trace correctly identifying 76% of people with ACR ≥3.4 g/mol (microalbuminuria threshold) and dipstick ≥1+ correctly identifying 82% of people with ACR ≥34 g/mol. This
supports the use of dipsticks when ACR is not available.

Pathologic albuminuria was very common in both communities. Subtle levels were evident in some of the youngest children (aged ≈5 years), and there was a relentless increase in levels with increasing age (Fig 5). Overall, 28% of adults had microalbuminuria and 21% had overt albuminuria in community 1,25 and the respective rates in community 2 were 31% and 13%. A second screen in the first community 10-14 years after the first screen showed no change in rates and trends.

ACRs were higher in females than males until middle age. In addition to its associations with age and sex, ACR directly correlated with current body size, blood pressure, higher triglyceride levels, and levels of γ-glutamyltransferase, C-reactive protein, uric acid, homocysteine, fibrinogen, glucose, and hemoglobin A1c. ACR correlated with the presence of skin sores and scabies, persisting antibody to the M protein of group A hemolytic streptococcus,32 and a history of poststreptococcal glomerulonephritis.33 ACR also correlated with high levels of circulating immunoglobulins, as well as high-titer antibodies to cytomegalovirus and Helicobacter pylori.34 Furthermore, ACR in young adults, and most markedly in females, inversely correlated with birth weight; lower birth weights in turn were associated largely with intrauterine growth restriction.35,36 Finally, captured to date by anecdote rather than modeling, there is marked family clustering of renal disease.

Correlations of ACR with “traditional” cardiovascular risk factors are striking, and associations with markers of infection and inflammation are another shared feature of renal and cardiovascular risk. That link is supported by correlations of ACR with carotid intimal-media thickness.29 Associations of ACR with lower birth weights probably are driven in part by lower nephron numbers, which derive from intrauterine growth restriction.37 Blood pressure also correlated with lower birth weights, with the effect more marked in females.38 Very recent data show that cardiovascular and renal deaths in young adults in the same community are preferentially segregated among those of lower birth weight (Fig 6).39 The marked decrease in mortality of low-birth-weight infants between the 1960s and 1980s, a therapeutic triumph in itself, thus has illuminated the Barker hypothesis in the context of chronic disease deaths later in life.40 There is a notable deficiency of the D allele of the angiotensin-converting enzyme gene in one of the communities,41 and a particular polymorphism in the p53 gene associates strongly with albuminuria in smokers in both communities (P < 0.01 for both), as well as with hemoglobin A1c level.42 Genome typing now is underway and will be evaluated against a cross-sectional phenotypic profile of those same individuals, as well as with their course over time.

The cross-sectional association of albuminuria with many factors suggests that renal disease in this setting is multideterminant, a model in which several nephropathic factors operating simultaneously progressively amplify the increase in albuminuria and loss of renal function that accompany increasing age. Specific models have been developed showing interactions of anti-group A hemolytic streptococcus antibody and higher body mass index32 and lower birth weights with higher body mass index.36

Figure 5. Increase in urine albumin-creatinine ratio (ACR) with age.
The models predict a fairly low prevalence of renal disease in people with no risk factors and the almost inevitable presence of overt albuminuria by middle age in people with a full menu of risk factors. Nenov et al 43 subsequently postulated a “multihit” model of CKD that embodies the same concept.

Serum creatinine level (directly) and estimated glomerular filtration rate (inversely) correlated with albuminuria with albumin excretion above the mid-microalbuminuria range. 25 However, creatinine-based glomerular filtration rate estimates probably underestimate renal impairment in remote-living Aboriginal people, who often have conspicuously lower muscle mass, at least in the extremities. A study of various glomerular filtration rate estimates versus gold-standard iothalamate clearances in Aboriginal people nationwide currently is in its third year. 44

NATURAL HISTORY

A follow-up study was conducted in the first community at a mean of 10.4 years after the first. Of 1,466 people in the first screen, baseline ACR predicted the later development of diabetes, clinical ischemic heart disease, and hospital admissions, including but not restricted to those related to cardiovascular causes. 26,45-47 There were 110 nonrenal natural deaths and 32 renal deaths in the interim, as well as 49 deaths of misadventure (accidents, suicide, homicide, poisoning, etc). Nonrenal natural deaths were predicted by baseline ACR over a continuum and renal deaths were predicted by high ACRs (generally ≥34 g/mol) at baseline (Fig 7). 26,31,48

In 1,029 survivors who participated in the second screen, ACR also had progressed. Table 1 lists proportions of people with ACR <3.4 g/mol at the first screen who had developed ACR ≥3.4 g/mol by the second screen. Such decompensation was evident even in the youngest participants and increased with age. It was higher in female children and adolescents than males, but the difference was less marked in adult life. Overall, including children, 26.5% of males and 35.2% of females had developed that end point during follow-up, whereas approximately 50% of adults had done so. Proportions of participants who had developed new-onset diabetes also were high, but were lower than proportions that developed albuminuria. The actual incidence rates of both outcomes are greater than those stated, given that the end points appeared at some undefined time during follow-up and people who had died a natural
death in the interim could not be included in the estimates. Of the simple parameters measured at the first screen, only age, female sex, and absolute value of baseline ACR predicted such progression.

**RENNAL MORPHOLOGIC EVALUATION**

In a review of all retrievable and assessable renal biopsy specimens from native kidneys performed on Aboriginal people across Australia from 1988 to 2004, we found (Table 2) that they had higher rates of diabetes than non-Aboriginal people undergoing biopsy, more frequently had heavy proteinuria, and had more advanced disease. Most biopsy specimens were from people living very remotely or remotely despite their smaller population size. They were younger at biopsy than those living less remotely, females predominated, and a substantial proportion of those with diabetes did not show diabetic changes in their biopsy specimens. There were many fewer biopsy specimens from Aboriginal people living closer to population centers despite their much larger population, they were closer to the age of non-Aboriginal people at biopsy, and, like them, showed a preponderance of males. In addition, most of those with diabetes had specific diabetic changes in their biopsy specimens.

All the usual morphologic “diagnoses” were otherwise represented to some degree. In addition to diabetic change, postinfectious change, lupus, infectious-related amyloid, and apparent reflux nephropathy were in relative excess, whereas proportions with immunoglobulin A nephropathy were lower. However, this does not imply fewer cases, given the overall excess of renal disease in Aboriginal individuals.

Biopsy specimens from Aborigines in remote and very remote areas usually showed glomerulomegaly, which was identified subjectively at first and confirmed through formal measurement (Fig 8). This confirms our report 12 years ago of glomerulomegaly and attendant focal glomerulosclerosis in biopsy specimens from Aboriginal people in the Top End of the Northern Territory49,50 and supports descriptions of

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**Table 1. Proportion (Percent) of Participants With New-Onset ACR ≥3.4 g/mol or Diabetes at 10.4 Years of Follow-up**

<table>
<thead>
<tr>
<th>Age Group at First Screen (y)</th>
<th>Males New Cases</th>
<th>Females New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Onset ACR ≥3.4 g/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>10.8 (10/93)</td>
<td>21.9 (21/96)</td>
</tr>
<tr>
<td>10-19</td>
<td>15.6 (21/135)</td>
<td>37.1 (26/70)</td>
</tr>
<tr>
<td>20-29</td>
<td>43.2 (41/95)</td>
<td>48.1 (25/52)</td>
</tr>
<tr>
<td>30-39</td>
<td>50.0 (18/36)</td>
<td>35.0 (14/40)</td>
</tr>
<tr>
<td>≥40</td>
<td>64.3 (9/14)</td>
<td>53.9 (14/26)</td>
</tr>
<tr>
<td>All</td>
<td>28.5 (99/373)</td>
<td>39.2 (100/284)</td>
</tr>
</tbody>
</table>

| New-Onset Diabetes           |                 |                   |
| 5-9                          | 0.9 (1/106)     | 2.6 (3/117)       |
| 10-19                        | —               | 12.4 (11/89)      |
| 20-29                        | 12.2 (17/139)   | 22.4 (23/102)     |
| 30-39                        | 17.7 (14/79)    | 32.1 (25/78)      |
| ≥40                          | 45.0 (18/40)    | 46.2 (30/65)      |
| All                          | 9.7 (50/515)    | 20.4 (92/451)     |

Note: Values expressed as percentage (number/total number).

Abbreviation: ACR, albumin-creatinine ratio.

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**Table 2. Demographic and Clinical Features of Indigenous Australians in the Nationwide Biopsy Series**

<table>
<thead>
<tr>
<th></th>
<th>Female (%)</th>
<th>Age at Biopsy (y)*</th>
<th>Diabetic at Biopsy (%)</th>
<th>Nephrotic Proteinuria (%)</th>
<th>Renal Failure at Biopsy (%)</th>
<th>Glomerular Volume (μm² × 10⁵)*</th>
<th>IgA Nephropathy (%)</th>
<th>Post-infectious GN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal, very remote (n = 386)</td>
<td>54.7</td>
<td>39.8 (20.5)</td>
<td>39.6</td>
<td>43.2</td>
<td>20.7</td>
<td>2.4 (2.3-2.5)</td>
<td>24.3</td>
<td>12.4</td>
</tr>
<tr>
<td>Aboriginal, remote (n = 65)</td>
<td>60.0</td>
<td>38.6 (17.6)</td>
<td>57.4</td>
<td>44.3</td>
<td>31.2</td>
<td>2.5 (2.2-2.8)</td>
<td>40.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Aboriginal, other (n = 84)</td>
<td>44.1</td>
<td>42.9 (18.6)</td>
<td>48.2</td>
<td>34.6</td>
<td>33.3</td>
<td>2.0 (1.8-2.3)</td>
<td>41.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Nonindigenous (n = 253)</td>
<td>39.9</td>
<td>46.0 (23.9)</td>
<td>14.3</td>
<td>21.9</td>
<td>16.7</td>
<td>2.0 (1.8-2.1)</td>
<td>11.7</td>
<td>22.1</td>
</tr>
</tbody>
</table>

Abbreviations: GN, glomerulonephritis; IgA, immunoglobulin A.

*aMedian (interquartile range).

*bGeometric mean (95% confidence interval).

Metropolitan or inner regional or outer regional.
glomerulomegaly in even earlier reports.\textsuperscript{51,52} However, glomerular enlargement was not prominent in Aborigines from major cities and inner and outer regional areas.

The disproportionately high number of biopsy specimens from Aboriginal people in remote and very remote areas despite their smaller population and younger average age at biopsy reflects their greater susceptibility to renal disease, which is mirrored in much higher ESRD rates. It is likely that glomerulomegaly marks this accentuated susceptibility, which is apparently more marked in females than in males. Aboriginal people living in major cities and inner and outer regional centers seem to have patterns and rates more compatible with those of non-Aboriginal Australians, including older age at biopsy, excess of males, and less likelihood of glomerulomegaly.

Obesity, current body size more generally, metabolic syndrome, diabetes, and nephron number are all determinants of glomerular volume.\textsuperscript{53-55} Glomerular enlargement beyond a critical point predisposes to focal, then global, glomerulosclerosis.\textsuperscript{50} We propose that the glomerulomegaly noted in biopsy specimens from remote and very remote-living Aboriginal people is driven largely by nephron deficiency and that nephron deficiency underlies their susceptibility to renal disease and hypertension. This is supported by findings at forensic (coronial) autopsy\textsuperscript{55-59} that remote-living Aboriginal adults from the Northern Territory tend to have smaller kidneys than other adults in the series and have on average about 180,000 fewer glomeruli per kidney: a mean of 711,466 (95% confidence interval, 571,498-851,433) versus 892,712 (95% confidence interval, 857,298-928,127), adjusted for age and sex ($P = 0.014$); Fig 9). Glomeruli also were larger.\textsuperscript{55-59} Furthermore, Aboriginal people with the lowest nephron numbers had higher rates of hypertension before death, whereas those with robust nephron numbers in the context of body size had low rates of hypertension.\textsuperscript{59}

Intrauterine growth restriction, which is reflected in low birth weight and was very common in Aboriginal Australia several decades ago, is almost certainly a major cause of this nephron deficiency in remote-living Aboriginal people.\textsuperscript{60,61} However, some degree of lower endowment might have been appropriate in relation to their body habitus, growth trajectories, and metabolic needs historically. We postulate that nephron deficits probably are less marked in urban Aborigines, who have much lower

![Figure 8. Distribution of mean glomerular volume (MGV) in renal biopsy specimens from Aboriginal people by category of remoteness and comparison with non-Aboriginal Australian biopsy specimens.](image1)

![Figure 9. Distribution of glomerular number in right kidney at coronial autopsy, Aboriginal versus non-Aboriginal.](image2)
rates of intrauterine growth restriction\textsuperscript{60} and greater degrees of ancestral admixture.

**MANAGEMENT AND HEALTH SERVICES POLICY**

Treatment of people with albuminuria or hypertension with angiotensin-converting enzyme inhibitors reduces progression of renal disease. It also decreases rates of renal failure and nonrenal natural death.\textsuperscript{62,63} In the original demonstration project, the number of people with overt albuminuria needed to treat over 3.5 years to avoid one terminal event was only 9.5. Treatment saves major costs in terms of dialysis avoided or delayed\textsuperscript{64} and postponement of premature death. When systematic screening and treatment are diminished, good clinical outcomes are lost.\textsuperscript{65}

These experiences have helped inform chronic disease management in Aboriginal health care delivery,\textsuperscript{23,66} resulting in a groundswell of altered practice in the last 10 years. Protocols for regular integrated screening for chronic disease, including hypertension, renal disease, diabetes, cardiovascular risk, and chronic lung disease, are embedded in standard health care plans within the primary care structure of most health services for Aboriginal people. The federal government has introduced reimbursement for Medicare Australia service items for regular (every 2 years) integrated screening of all adults for chronic disease and for treatment of people with defined conditions. Medicines for people in remote areas are supplied free under an additional federal government initiative, Section 100,\textsuperscript{57} and there has been a massive increase in prescription of chronic disease medications. The central role of the indigenous health care workers in these programs is acknowledged. Furthermore, electronic information systems are being introduced progressively, with processes for constant evaluation and reporting. Finally, the need for therapy with multiple drugs is acknowledged, a trial of a polypill variant is underway, and sustained drug-delivery systems (eg, patches) are at least under discussion. Many challenges persist, including lack of infrastructure and personnel in remote areas, but there is a real sense of optimism and confidence in the government’s commitment for ongoing change. Finally, a trial of pharmacologic prevention of new-onset albuminuria and hypertension now is underway. True primary prevention will depend on sustained improvements in socioeconomic circumstances and community infrastructure, health services, and birth weights.

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**REFERENCES**


33. Hoy WE, Coles K. Helicobac-

34. Hoy WE, Kile E, Rees M, Mathews JD. Low birth weight and renal disease in Australian Aborigi-


