Review Article

Renal disease and the environment: lessons from Aboriginal Australia*

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SUMMARY: Aborigines in remote Australia are living in profound socio-economic disadvantage and epidemiological transition. They are also experiencing an epidemic of cardiovascular disease, with deaths increased >threefold and renal failure increased >20-fold. Dialysis costs pose a crisis, but premature death is the greater human catastrophe. In one high-risk group, we identified renal disease through the urinary albumin/creatinine ratio and assessed its distribution, its correlations, its associations with other morbidities and overall mortality and its natural history. We later introduced systematic antihypertensive and renal-protective treatment for afflicted persons. Albuminuria was detected in 55% of adults. It was inversely correlated with glomerular filtration rate (GFR) and generally progressed over time. It was strongly correlated with cardiovascular risk, and its intensity predicted not only renal failure but also all-cause natural death. Factors correlated with renal disease included increasing age, low birthweight and infant malnutrition, adult weight gain and its syndrome X metabolic accompaniments, skin infections, post-streptococcal glomerulonephritis, heavy drinking, multiparity and a family history of renal disease. Nephron endowment probably also influences risk, with birthweight being one important driving force. Ironically, improved health services have probably contributed to the epidemic of renal failure in at least two ways: increased survival of low-birthweight infants and increased longevity in adults, allowing the full progression of renal disease to its terminal state. The treatment programme was associated with swift and massive reductions in end-stage renal failure, overall mortality and costs. Renal disease is multideterminant, with the simultaneous operation of several risk factors amplifying the increase in albuminuria and decrease in GFR that accompany increasing age. While many risk factors and mechanisms remain to be identified, our findings provide ample grounds for immediate intervention in similarly afflicted communities, with expectation of excellent outcome. Improved services will probably result in additional ascertainment of disease and more opportunity for its expression, so that disease prevention and modification become even more pressing obligations. Major shifts in our political, social, academic and clinical priorities are needed to effectively address these issues for all Aboriginal communities.

KEY WORDS: Australian Aborigines, renal disease

INTRODUCTION

Australian Aborigines are a disadvantaged and marginalized people struggling to survive in a crisis of social and cultural transition. Most Aborigines in the Northern Territory live in remote areas, in serious poverty and disadvantage, with inadequate services of all sorts. Health services are uneven: excellent care for acute and advanced illnesses and for catastrophes is rendered in centralized hospitals, but at the community level, environmental health, health education and primary care are poorly resourced, and ‘lifestyle’ or non-communicable adult diseases have been relatively neglected.

Mortality rates reflect this sociological disaster. Standardized mortality rates in Aboriginal adults in the Northern Territory actually rose between 1981 and 1992, to a level more than five times that of non-Aboriginal Australians. Premature death in young and middle-age adults is contributing to family, community and cultural breakdown. Most major conditions are represented in this excess mortality, including intoxications, trauma, cardiovascular disease, diabetes, lung disease and infec-
sorts, endemic and epidemic post-streptococcal glomerulonephritis, excessive adult weight gain with its syndrome X metabolic accompaniments, lung disease, heavy drinking and high rates of smoking.7–9

Renal disease, as evidenced by an increased urinary albumin/creatinine ratio (ACR, g/mol), was pervasive, with only 29% of adults (20+ years) having a ‘normal’ ACR (<1.1), while 23% had microalbuminuria (ACR 3.4–33) and 30% had overt albuminuria (ACR 34+).8,9

We have studied the renal disease that underlies this epidemic of renal failure, with the principal purpose of identifying solutions. Along the way we have illuminated risk factors, and mechanisms, for disease that can probably be generalized not only to other high-risk groups, but to the broader population.

STUDIES IN A HIGH-RISK COMMUNITY

The study was based in a remote island community (population about 1680, >80% participation) whose annual ESRD incidence peaked at 2706 per million between 1993 and 1996, and whose recent cardiovascular death rates are six times those of an age-matched affluent non-Aboriginal population living in Canberra, Australia’s capital.6 In a simple clinical and biochemical examination, we identified pathology in abundance: low birthweight, childhood malnutrition, infections of many sorts, endemic and epidemic post-streptococcal glomerulonephritis, excessive adult weight gain with its syndrome X metabolic accompaniments, lung disease, heavy drinking and high rates of smoking.7–9

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On cross-sectional review of the community profile, there was a progressive increase in ACR with increasing age (Fig. 2). There was a hint of higher estimated glomerular filtration rates (GFRs)10 in individuals with subtle levels of pathological albuminuria and clearly
lower GFRs in individuals with progressively higher levels of overt albuminuria (Fig. 3). In a longitudinal study of 581 adults (follow-up 1–8 years, mean 3.9 years), ACR increased and GFR fell in individuals with time, at rates that were strongly correlated with the severity of disease at baseline. Renal failure developed only in people with ACR levels > 100 g/mol at baseline.11

The intensity of baseline ACR was associated not only with renal disease and its progression, but also, over a continuum, with subsequent natural deaths (Fig. 4). These deaths included, but were not restricted to, cardiovascular deaths. This association persisted after accounting for age and sex, with a hazard ratio (95% CI) of 3.5 (0.8–15.3) in persons with microalbuminuria compared with those of lower ACRs and of 7.8 (1.9–33.2) for those with overt albuminuria at baseline. Thus, ACR is an indicator of mortality rate in this population.11,12

Using the ACR as a continuous and categorical variable, we evaluated its correlations with clinical and biochemical parameters measured in the screening examination. This list is not exhaustive, because the associations probed were constrained by the hypotheses proposed and the limited tools and resources available for their study. Factors that correlated significantly with ACR, and therefore with loss of renal function, cardiovascular disease and risk of natural death,8–14 were as follows:

1. ageing;
2. low birthweight and infant malnutrition;
3. adult weight with excessive central fat deposition, and its attendant high blood pressure, dyslipidaemia, hyperinsulinaemia, dysglycaemia and diabetes;
4. infections, including skin sores and scabies;
5. remote episodes of post-streptococcal glomerulonephritis;
6. heavy drinking, marked by a high γ-glutamyl transferase level;
7. multiparity in women (≥ 3 children); and
8. a family history of renal disease.

Estimates of risk enhancement for the presence of overt albuminuria associated with various ‘diagnoses’ in these categories are substantial, and have been reported previously.8,9

We thus propose a multideterminant rather than single-cause model of renal disease in which the simultaneous operation of several risk factors progressively enhance the increase in albuminuria that accompanies increasing age. Figure 5, predicted from a multivariate model,8,9 illustrates this phenomenon in all adults. It shows that overt renal disease is almost inevitable by middle life in people with a full menu of risk factors (a fairly common situation), and that rates of renal disease in persons with no risk factors are much lower at all ages, although still substantial. Figure 6a and b illustrates this phenomenon for adults in whom birthweights were recorded, and shows why the effects of a single risk factor (in this case low birthweight), might be obscured or overlooked in a low-risk environment.14 A similar amplifying

Fig. 3 Correlation between albumin/creatinine ratio and glomerular filtration rate on baseline screen (adjusted for age, sex and body-mass index).

Fig. 4 Albumin/creatinine ratio and cumulative mortality for natural deaths (adjusted for age and sex).

Fig. 5 Predicted probability of overt albuminuria in adults.
adjusted kidney volume and birthweight in children in this community (Fig. 7), which supports a link between nephron endowment and intrauterine growth. In view of the fourfold difference in nephron number described in the general population, any hypothetical nephron ‘deficit’ might also have a genetic component. This is likely to be adaptive; a smaller number of nephrons might have been entirely adequate in the previous subsistence state, or even a survival advantage in conditions of salt and water deprivation.

Our studies suggest that reduced nephron endowment or impaired nephron maturation might predispose to renal disease. These findings are reflected in the lower renal mass in autopsy studies and lower renal volume on ultrasound in some Aboriginal people. This is probably related, in part, to intrauterine growth retardation and infant malnutrition. We have demonstrated a continuous relationship between body-surface-area-adjusted kidney volume and birthweight in children in this community (Fig. 7), which supports a link between nephron endowment and intrauterine growth. In view of the fourfold difference in nephron number described in the general population, any hypothetical nephron ‘deficit’ might also have a genetic component. This is likely to be adaptive; a smaller number of nephrons might have been entirely adequate in the previous subsistence state, or even a survival advantage in conditions of salt and water deprivation.

Findings in ‘diseased’ Aboriginal biopsies are compatible with these hypotheses. All the usual morphological

model can be constructed for the risk of microalbuminuria in young persons (<30 years) based on interactions of age, female sex, blood pressure and a remote history (>4 years previously) of post-streptococcal glomerulonephritis.

Fig. 6 (a) Amplification of albuminuria: low birthweight as one of several risk factors. (b) Amplification of albuminuria: low birthweight as a sole risk factor.

Fig. 7 Ultrasound estimates of kidney volume, adjusted for body surface area, in Aboriginal children.

Fig. 8 Natural deaths and end-stage renal disease, natural history vs ‘intention to treat’.
diagnoses are represented, but the diversity of findings and lack of specificity of many biopsies make them a poor fit for particular morphological or ‘aetiological’ categories.\textsuperscript{18–20} The single consistent finding is glomerulomegaly, often with other changes than glomerular sclerosis.\textsuperscript{18–20} This probably represents excessive nephron hypertrophy, resulting perhaps from an excess of trophic factors in the post-natal environment, as well as compensatory hypertrophy in individuals with reduced nephron numbers. Hyperperfusion and progressive sclerosis in excessively hypertrophied nephrons provide theoretical mechanisms for increasing albuminuria and accelerated nephron death.

Health and community services exert a powerful influence on the expression of renal (and other chronic) diseases, by influencing risk factors, natural history and survival. Risk is reduced by environmental improvements, better infant and childhood nutrition, antiscabies programmes and containment of epidemics of post-streptococcal glomerulonephritis, while a vaccine against nephritogenic streptococci is eagerly awaited. Paradoxically, however, improved services can facilitate disease expression. Dramatic reductions in infant mortality since the 1960s, due to better hospital management of sick babies, have resulted in large cohorts of low-birthweight infants now surviving to adult life\textsuperscript{13,14} who are at high risk of renal and other chronic diseases. This phenomenon will abate if birthweights continue to improve. In addition, better management of infections, diabetes, cardiovascular morbidity (angioplasties, bypass procedures, etc.) in high-risk patients, and progressive effacement of the 20+ year mean survival differential between Aborigines and non-Aboriginal Australians through general improvements in health will lend more opportunity for nephropathy to run its fairly slow course to renal failure.

These considerations underpin arguments to systematically detect and modify disease progression in people already afflicted, the ultimate deliberate environmental influence. To this end, we introduced a treatment programme into the study community in late 1995, using the long-acting angiotensin-converting enzyme (ACE) inhibitor perindopril (Coversyl, Servier, Australia) as the primary agent.\textsuperscript{21–25} Eligibility criteria were hypertension (systolic blood pressure $\geq 140$ or diastolic blood pressure $\geq 90$ mmHg), diabetes with ACR 3.4+ (microalbuminuria threshold) regardless of blood pressure and overt albuminuria (ACR 34+) that was progressing regardless of blood pressure and diabetes status.

By December 1998, 240 people, or 26% of the entire adult population, had enrolled: 46% were diabetic, 64% hypertensive and 67% had overt albuminuria. Participation was enthusiastic, and compliance good in 70%.\textsuperscript{24} Analysis at 3 years showed a dramatic and sustained fall in blood pressures, and stabilization of ACR (previously rising) and of GFR (previously falling) on a group basis. It also showed an estimated 62% reduction in combined endpoints of natural death and renal failure when compared with an historical cohort matched for disease severity in the pre-programme era. Such benefit applied at all levels of disease severity in persons with overt albuminuria, in whom most of the events were segregated, is shown in Fig. 8. Community rates of ESRD and natural deaths support these estimates. We estimate savings on dialysis costs alone in this small community between A$700 000 and A$3.1 million, in the first 3 years of the programme, depending on whether ESRD and death rates would have continued to escalate or achieved a plateau in its absence.\textsuperscript{25} The reduction in morbidity and mortality is, however, the greater human gain.

CONCLUSIONS

Renal disease in this population is multideterminant, with the excess of disease associated with a high density and multiplicity of nephropathic factors operating in a high-risk environment. Renal disease is intimately related to the general health profile and other chronic ‘disease’ states, and tightly correlated with overall mortality.\textsuperscript{26} Risk factors derive from, or are exacerbated by, rapid transition, poverty and disadvantage, and the deficiencies and successes of health services. Environmental factors have undoubtedly also influenced genotypes over time.

Prevention depends on sustained improvements in socio-economic circumstances, infrastructure and health services. Concerns over ESRD treatment costs might yet prompt such changes. For persons already afflicted, disease is easily diagnosed and progression is dramatically altered by interventions within our reach.\textsuperscript{27} Control of blood pressure, adult weight and infections are especially important. Pharmacological intervention will postpone ESRD and reduce premature death in early and middle adult life, and might postpone renal failure beyond reasonable life expectancies in many people.

Meanwhile, we must advocate for intersectoral initiatives to improve the environmental and socio-economic circumstances of high-risk populations. In our academic domains, we should foster interspecialty collaboration with the aim of developing a coherent unified approach to these health issues. We must redirect significant intellectual and material resources from expensive high-technology, diagnostic and interventional tracks in metropolitan hospitals towards issues of prevention and disease modification. Sociological, public health and community perspectives should be incorporated into specialist training, and mentorship and granting arrangements fostered in these disciplines. We should develop community-based health protocols, with defined goals, and accountability for outcomes. Improved health, greater longevity and reduced health care costs can probably be achieved over a shorter term than ever imagined.
REFERENCES