Reduced nephron number and glomerulomegaly in Australian Aborigines: A group at high risk for renal disease and hypertension

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Aborigines in remote areas of Australia have much higher rates of renal disease, as well as hypertension and cardiovascular disease, than non-Aboriginal Australians. We compared kidney findings in Aboriginal and non-Aboriginal people in one remote region. Glomerular number and mean glomerular volume were estimated with the disector/fractionator combination in the right kidney of 19 Aborigines and 24 non-Aboriginal people undergoing forensic autopsy for sudden or unexpected death in the Top End of the Northern Territory. Aborigines had 30% fewer glomeruli than non-Aborigines – 202 000 fewer glomeruli per kidney, or an estimated 404 000 fewer per person ($P = 0.036$). Their mean glomerular volume was 27% larger ($P = 0.016$). Glomerular number was significantly correlated with adult height, inferring a relationship with birthweight, which, on average, is much lower in Aboriginal than non-Aboriginal people. Aboriginal people with a history of hypertension had 30% fewer glomeruli than those without – 250 000 fewer per kidney ($P = 0.03$), or 500 000 fewer per person, and their mean glomerular volume was about 25% larger. The lower nephron number in Aboriginal people is compatible with their susceptibility to renal failure. The additional nephron deficit associated with hypertension is compatible with other reports. Lower nephron numbers are probably due in part to reduced nephron endowment, which is related to a suboptimal intrauterine environment. Compensatory glomerular hypertrophy in people with fewer nephrons, while minimizing loss of total filtering surface area, might be exacerbating nephron loss. Optimization of fetal growth should ultimately reduce the florid epidemic of renal disease, hypertension, and cardiovascular disease.

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An epidemic of renal failure has appeared over the last 20 years among Aborigines living in remote areas of Australia. The average current incidence of treated end-stage renal disease exceeds 1500 per million and the age-adjusted rate is more than 20 times than that of non-Aboriginal Australians, whereas the incidence approaches 3000 pm in some communities.[1,2] Pathologic albuminuria or proteinuria, which marks the underlying renal disease, is pervasive in all remote communities that have been studied, with rates and levels increasing with age.[3–9] An epidemic of cardiovascular disease, type II diabetes, and hypertension has developed in parallel and cardiovascular disease is now the leading cause of death, with rates three to six times those of non-Aboriginal people.[10,11] Renal disease is intimately related to these conditions, and all can be understood in the context of the rapid epidemiologic transition these people have experienced in the last four or five decades, and their current profound socioeconomic disadvantage.[3,4,12–15]

Our studies show that renal disease in the Aboriginal community setting is multideterminant, with a multitude of risk factors operating across the life course to amplify progressively renal injury and the loss of renal function that accompanies increasing age.[4] Others have proposed a similar concept.[16] We have demonstrated that low birthweight is one important risk factor operating in the Aboriginal environment, and proposed it might act through reduced nephron endowment.[17,18]

Some years ago, Brenner *et al.*[19] proposed that reduced nephron endowment might be a fundamental cause of essential hypertension, and might also predispose to renal insufficiency.[20] Furthermore, they proposed that both these processes might be exacerbated by accelerated loss of remaining nephrons owing to hyperperfusion injury of glomeruli that had undergone compensatory hypertrophy.[21]

In a study of 78 coronial (forensic) series of autopsies from the USA and Australia (now updated to 220), we

described a 10-fold range in nephron numbers in kidneys of 'normal' people, and proposed that those at the lower end of the spectrum may be predisposed to kidney failure on the basis of reduced nephron endowment.[22] We described a progressive loss of glomeruli over the course of adult life, and a strong inverse correlation between average glomerular volume and nephron number, which probably represents compensatory hypertrophy in remaining nephrons when numbers are limiting. Furthermore, we showed in the US subjects that birthweight over a continuum was a powerful determinant of nephron number and, inversely, of glomerular volume.[23]

Recently, Keller *et al.*[24] demonstrated a dramatically lower number of nephrons in people with essential hypertension, with enlargement of glomeruli that remained. These phenomena, although somewhat less pronounced, were then confirmed among Whites in the US autopsy series.[25,26] In all these instances, the presumed compensatory hypertrophy in residual glomeruli tended to 'restore' total glomerular volume towards more 'normal' values than the lower nephron number would predict.

In this report, we analyze findings in Aboriginal people from the US/Australian study and speculate how the observations might relate to disease susceptibility.

RESULTS

Most of the observations described for the entire series[22] applied for the Australian series separately. Nephron number tended to be lower in females than in males, by 11% in the combined ethnic groups, and by 5% in Aboriginal people specifically, but the differences were not significant ($P = 0.40$ and 0.63, respectively). Mean glomerular volume and kidney mass did not differ significantly by sex. Nonetheless, all comparative analyses were adjusted for sex as well as age.

Figure 1a shows the loss of glomeruli during adult life, Figure 1b shows the inverse correlations between mean glomerular volume and glomerular number, and Figure 1c shows the strong influence of body size on kidney weight.

There were only six available birthweights in the Australian series, which was insufficient for meaningful analysis. The five available birthweights for Aboriginal people were 1.81, 2.4, 2.665, 2.88, and 4.01 kg, with a mean of 2.75 (s.d. 0.8) kg. This is 600 g less than the current Australian average birthweight, and is precisely the average of young adults in the community in which birthweight effects have been studied most thoroughly, where 35% of people aged 20–39 years had weighed <2.5 kg at birth.[4,17,18,27–29] However, glomerular number was strongly related to height in adults (Figure 1d), which birthweight predicts.[30] In this analysis, height contributed two-thirds of the explained variance in glomerular number.

Table 1 compares characteristics of the participants in the Australian series by ethnic group. There was a greater proportion of females in the Aboriginal group, reflecting higher rates of unexplained or sudden death in Aboriginal than non-Aboriginal females. Aborigines were also younger at the time of death on average, and were lighter and shorter than non-Aboriginal people. Table 2 shows that they had, on average, 202 000 fewer glomeruli in a single kidney than non-Aboriginal people (or about 30% fewer), and their mean glomerular tuft volume was significantly larger (by about 27%). Their kidney weight was significantly lower. Their

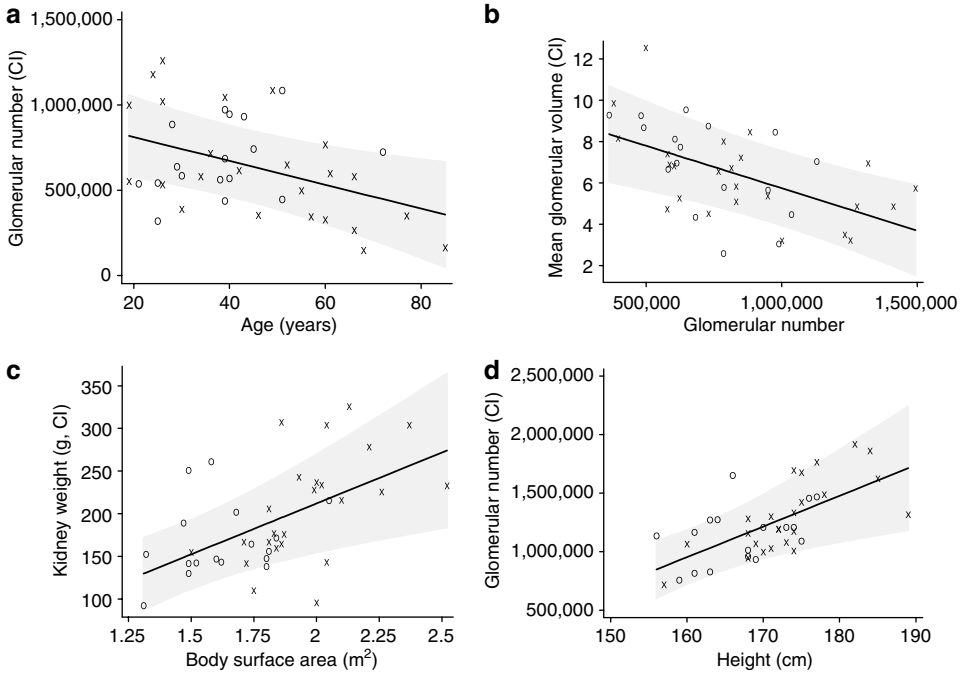

Figure 1 | Autopsy findings, right kidney, in adults (18 + year) in the Australian series, adjusted for age, sex, and race. (0) Aboriginal; (x) non-Aboriginal.

estimated total glomerular mass, which is not an independent measurement, but the product of glomerular number and mean glomerular volume, did not differ, implying that glomerular hypertrophy adequately compensated the reduction in filtering surface threatened by reduced glomerular number. There was no difference in the proportions of glomeruli that were sclerosed, nor in the amount of cortical fibrosis (not shown), which paralleled glomerulosclerosis very closely.

Figure 2 demonstrates the different distribution of kidney characteristics in the Australian series. There was a significant leftwards shift of glomerular number among Aborigines, a rightward shift in mean glomerular volume, and a leftward shift in kidney mass. However, the distributions of the percentage of sclerosed glomeruli were similar.

Fourteen Aboriginal adults had a fairly reliable clinical history, allowing allocation of a diagnosis of hypertension in five. Those with a history of hypertension had significantly fewer glomeruli than those without (Figure 3a), whereas their mean glomerular volume tended to be larger (Figure 3b). As a result, estimated total glomerular volume did not differ significantly, at 5.9 cm^3 (95% confidence interval 4.5–7.3) for those without hypertension and 5.7 (3.8–7.6) for those with hypertension, $P = 0.87$.

There were no differences in glomerular number according to the presence of ischemic heart disease in Aborigines. This applied whether the death was finally attributed to ischemic heart disease and coronary atherosclerosis, and whether people with an 'incidental' finding of moderate or severe coronary artery disease at autopsy were also included.

Table 1 | Characteristics of adult participants, Aboriginal vs Non-Aboriginal people

	Aboriginal, *n*=17	Non-aboriginal, *n*=24	*P*-value
Male:female	11:6	21:3	
Age (year)	38.5 (12.4)	46.8 (19.0)	*P*=0.124
Height (cm)[a]	168.1 (166–171)	172.7 (170–174)	*P*=0.0109
Weight (kg)[a]	58.9 (51–67)	79.0 (73–85)	*P*=0.0006
BMI (kg/m^2)[a]	20.8 (18.1–23.5)	26.6 (24.4–28.9)	*P*=0.0034
BSA (m^2)[a]	1.65 (1.54–1.76)	1.95 (1.86–2.04)	*P*=0.0003

BMI, body mass index; BSA, body surface area.
[a]Adjusted for age and sex.

DISCUSSION

Aboriginal people in the Northern Territory of Australia who underwent forensic autopsy for sudden or unexpected death, without an advance suspicion of renal disease, had significantly fewer nephrons than non-Aboriginal people undergoing autopsy at the same center. They also had a larger mean glomerular volume. In addition, Aboriginal adults with a history of hypertension had significantly fewer nephrons than Aborigines without a history of hypertension, and the glomeruli of those nephrons were, on average, larger.

Rates of renal failure in Aboriginal people from this region are among the highest in Australia,[1] and adults in every community tested have very high rates of albuminuria.[8,9] It is probable that reduced nephron number is contributing to the accentuated susceptibility to renal disease and to its progression.[20] The association of lower nephron numbers in Aboriginal people with hypertension is a direct confirmation of a relationship long suggested:[19] it supports the observations of Keller *et al.*[24] in Europe, and more recently of Hughson *et al.* in the US autopsy series,[25,26] and is compatible with the high rates of hypertension in the Aboriginal population.[8,9]

The larger mean glomerular volume in Aboriginal people in general, and in those with hypertension in particular, is consistent with compensatory hypertrophy of remaining

Table 2 | Characteristics, right kidney, Aboriginal vs non-Aboriginal people

	Aboriginal	Non-aboriginal	*P*-value
Kidney weight (g)			
Range	97–246	95–326	*P*=0.019*
Mean (95% CI)*	160.4 (131–189)	209.1 (185–223)	
Nglom			
Range	364 262–1 129 233	380 517–1 493 665	*P*=0.036
Mean (95% CI)*	683 174 (552 954–813 393)	885 318 (770 885–999 751)	
Vglom ($\mu m^3 \times 10^6$)			
Range	4.7–11.1	3.3–13.4	*P*=0.022
Mean (95% CI)*	8.4 (7.3–9.5)	6.6 (5.7–7.5)	
Vglomtot (cm^3)			
Range	4.7–10.4	2.7–11	*P*=0.79
Mean (95% CI)*	5.7 (4.7–6.7)	5.5 (4.7–6.4)	
Glomerulosclerosis (%)			
Range	0–8.7	0–12.2	*P*=0.82**
Median, IQR	1.68 (0.6–5.2)	1.52 (0.8–4.7)	

CI, confidence interval; IQR, interquartile range; Nglom, glomerular number; Vglom, mean glomerular volume; Vglomtot, total glomerular volume.
*Average values adjusted for age and sex.
**By rank-sum test.

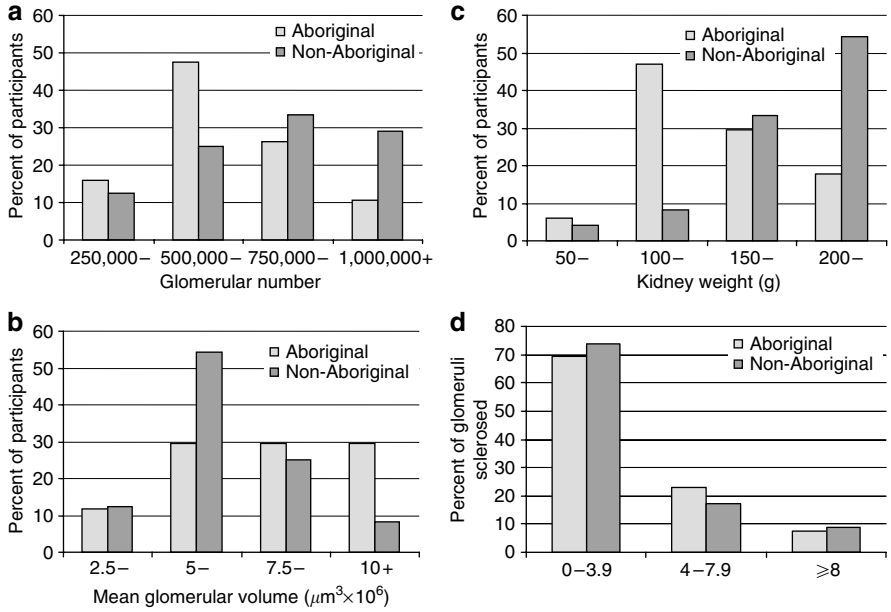

Figure 2 | Distribution of findings in the right kidney by category, Aboriginal vs non-Aboriginal adults.

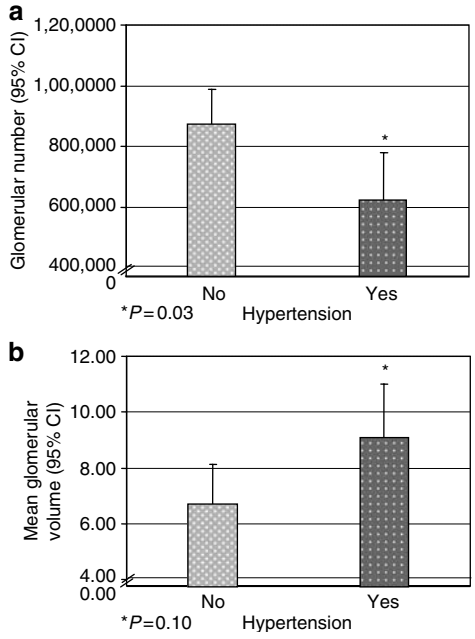

Figure 3 | Kidney characteristics in adults Aborigines with and without hypertension, adjusted for age and sex.

nephrons in situations of nephron deficit. This process seems to reasonably compensate total glomerular mass, at least in most people and for some time. It is not known whether hyperfusion injury operates on a continuum or becomes manifest at some critical glomerular size. However, the range of glomerular volumes disguised by the 'mean' value for each kidney is large,[31] and in people with large mean values the maximum might be very large indeed.

The similar proportions of sclerosed glomeruli in the two groups argue against an excessive loss of nephrons as the major cause of the reduced glomerular number in the Aboriginal group, supporting the hypothesis that the lower glomerular numbers are largely related to reduced nephron endowment. While acknowledging possible genetic and long-term adaptive influences on kidney development, the major cause is probably limitation of kidney development through a suboptimal intrauterine environment.[32–38] This is most commonly associated with generalized intrauterine growth restriction. Major agents or associations include small maternal size, particularly with low weight for height, which is the major cause of low birthweight internationally,[39,40] global malnutrition or micronutrient deficiency (with Vitamin A deficiency a likely candidate), and smoking. The impact of maternal smoking is huge, with estimates that fetal weight is reduced by 10–15 g/cigarette smoked per day.[39–42] Fetal growth is also restricted by hypoxia, infections, toxins, certain drugs, metabolic perturbations, including hyperglycemia, and probably psychosocial as well as physical stress. Finally, it is now known that nephrogenesis does not proceed optimally after premature birth, even in babies whose intrauterine growth was satisfactory until close to delivery.[43,44]

All of these factors operate at high density in the remote Aboriginal community setting. Frank hunger is common and the global diet is of poor quality, with fresh fruit and vegetables particularly lacking. Infections are many and social and psychological stresses often severe. In a study of Aboriginal children born in remote communities across the NT in the late 1980s and early 1990s,[37,38] 27.5% were small for gestational age and 10.3% were premature births; 31% of the 473 mothers were 'underweight' by Australian standards

(body mass index $< 20\,kg/m^2$); and 16% met the WHO standards for malnutrition for women (body mass index- $< 18.5\,kg/m^2$); 18.5% were under 18 years of age, whereas 56% smoked and 15% drank alcohol while pregnant.[45–47] Smoking was associated with intrauterine growth restriction, whereas low maternal body mass index, as well as drinking during pregnancy, were associated with relatively smaller kidneys and high rates of pathologic albuminuria in their offspring at ages 10–14 years.[48] The picture was scarcely better between 2000 and 2002, when Northern Territory-wide government data showed that 46% of all Aboriginal mothers smoked and 11.4% continued to drink alcohol while pregnant.

The autopsy results are compatible with epidemiologic and clinical data. In the community setting, young adult people with lower birthweights have higher rates of pathologic albuminuria and higher blood pressures than those with normal birthweights.[17,18,27] Children of lower birthweight have smaller kidneys than those of higher birthweights,[28] and adults with smaller kidneys have higher blood pressures and rates of albuminuria than those with larger kidneys.[29] The glomerular enlargement associated with reduced nephron number is compatible with the marked glomerulomegaly seen in most kidney biopsies from Aboriginal people with clinical renal disease from this region, and with the progressive glomerular sclerosis which accompanies it.[49,50]

Ironically, improvements in health care have probably contributed to the current chronic disease epidemic. Owing to better care of sick infants, infant mortality in Aborigines in the Northern Territory fell from about 160/1000 births in the early 1960s to about 28/1000 now, with most of the prior excess deaths and subsequent retrieval among infants with intrauterine growth restriction. Thus, large cohorts of low birthweight babies have survived to adolescence and adult life, potentially, at high risk for chronic diseases.[17,18,28,29,51]

The findings and the postulated pathways help explain the current epidemic of kidney and related chronic diseases in Aboriginal people, and point to obvious remedies. Body habitus cannot be substantially changed in an existing generation of adolescents and young women, and excessive weight gain itself exacerbates their own risk of chronic disease.[4,8,9] Optimal birthweights for Aboriginal children are not known. However, for those still unborn, a favorable intrauterine environment that promotes optimal organogenesis is obviously desirable. For people already alive, the challenge is to optimize survival of their existing nephrons, by avoiding postnatal renal insults, which abound in these environments (infections, poststreptococcal glomerulonephritis, malnutrition, toxins, drugs, smoking, alcohol abuse, acute renal failure), and by minimizing metabolic and vascular stressors. As for the broader population, one fundamental challenge is avoiding excessive weight gain. Additional benefits might accrue from a well-rounded diet-rich in antioxidants.[52] For very high-risk communities, a trial of medical prophylaxis is planned. Finally, vigorous and appropriate renal and vascular sparing therapy for those who need it promises substantial delay or avoidance of morbidities, renal failure and premature death.[53,54]

MATERIALS AND METHODS

Participants were people subjected to autopsy for sudden or unexpected death at the Royal Darwin Hospital in the Northern Territory of Australia and at the University of Mississippi Medical Centre in Jackson, MS, USA. The handling and testing of kidneys has been described in detail previously.[55,22] Briefly, both kidneys were weighed, the right kidney was perfusion-fixed with formalin, and was systematically sampled for stereologic study. Mean glomerular volume and total glomerular number were estimated by the disector/fractionator combination. Kidney sections were examined by light microscopy (MDH), and the proportions of obsolete glomeruli and cortical atrophy were assessed in sections stained with Periodic Acid Schiff, Alcian Blue Hematoxylin, and Masson Trichrome.

For the Australian participants, autopsy findings were recorded and the causes of death were ascertained, initially through the local Coroner's records, and more recently through the National Coronial Information System. Enquiries about the previous health of the participants were made through the next-of-kin who gave consent, through medical records at the Royal Darwin Hospital, where available, and, for Aboriginal people, enquiries of the community clinics. A health history was more adequate in Aboriginal than in non-Aboriginal people; the latter had usually not been long-term residents in the area, they lacked local records, and their next-of-kin often knew little of their clinical histories. Aboriginal people were allocated a history of hypertension if their local clinic confirmed that such a diagnosis had been made in the past, the standard definition being a blood pressure $\geqslant 140/90$ mm Hg on at least two occasions. Attempts to gather birthweights were largely unsuccessful, in part, because these were not systematically recorded for Aboriginal people until the early 1970s.

The Australian series consisted of 19 Aborigines (18 adults, of 18+ year) and 24 non-Aboriginal people (all 18+ year). The Aboriginal people all came from remote areas. Clinical histories and coronial autopsy findings were not available for two. Of the 17 Aboriginal people (16 adults) with autopsy findings accessed, 12 died of natural causes (including a baby with sudden infant death syndrome) and five died deaths of misadventure (suicide, accidents, poisoning). Among the 11 deaths of adults attributed to natural causes, eight were associated with atherosclerotic vascular disease: six were attributed to ischemic heart disease/coronary atherosclerosis, alone in four, and in conjunction with pneumonia and drug toxicity (one each); an additional person died of a ruptured aortic dissection, and another died of pneumonia, with an old myocardial infarction. Among the five adults dying deaths of misadventure, one had mild and another had moderate coronary artery atherosclerosis.

The general features of the Australian data were assessed, then the Aboriginal and non-Aboriginal data were compared. This optimizes regional matching, involves a single harvesting center, and allows adjustments for differences in age, gender, and body size across ethnic groups.

Analyses were carried out with STATA statistical package, Version 8 (College Station, Texas, USA). Kidney data were analyzed as continuous and as categorical variables. Linear and polynomial multivariate regressions were used to assess the magnitude and strength of associ ations of kidney variables with one another and with other factors.

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