Renal biopsy findings among Indigenous Australians: a nationwide review

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Abstract

We summarise findings on 643 renal biopsies on Indigenous people across Australia, and compare them with 249 non-Indigenous biopsies. The relative population-adjusted biopsy frequencies were 16.9, 6.6 and 1 respectively, for Aboriginal people living remotely or very remotely (R/VR), for Torres Strait Islander people, and for non-remote-living Aboriginal people. Indigenous people more often had heavy proteinuria and renal failure at biopsy. No single condition defined the Indigenous biopsies, and where biopsy rates were high, all common conditions were in absolute excess. Indigenous people were more often diabetic than non-Indigenous people, but diabetic changes were still present in fewer than half their biopsies. They also had higher rates of segmental sclerosis, post-infectious glomerulonephritis, and mixed morphology. Among the great excess of biopsies in R/VR Aborigines, females predominated, with younger age at biopsy and larger MGVs. Glomerulomegaly characterized biopsies with mesangiopathic changes only, with IgA deposition or with diabetic change, and with focal glomerulosclerosis (FSGS). This series reveals great variations in biopsy rates and findings in Indigenous Australians. It refutes prevailing dogma that most indigenous renal disease is due to diabetes. Glomerulomegaly in R/VR Aboriginal people probably results from nephron deficiency related to low birth weight, contributes to accentuated susceptibility to kidney disease, and predisposes to FSGS.glomerulosclerosis (FSGS). This series reveals great variations in biopsy rates and findings among Indigenous Australians. It refutes prevailing dogma that most indigenous renal disease is due to diabetes. Glomerulomegaly in R/VR Aboriginal people probably results from nephron deficiency, in part related to low birth weight, contributes to the accentuated susceptibility to kidney disease, and predisposes to FSGS.

Introduction

It is well known that Australia's Indigenous people are experiencing an epidemic of hypertension, type 2 diabetes, cardiovascular disease, renal disease and renal failure (1,2). Renal disease has especially captured attention because of the high costs of treating subjects with renal replacement therapy (RRT). It is less well known that disease burden and outcomes differ markedly among Indigenous people across the country (3-9).

Figure 1 is a map of Australia by five categories of "remoteness" as defined by the Accessibility/Remoteness Index of Australia (ARIA)+ methodology (10). Most of the interior of the continent and the north and west are remote or very remote, as are the Torres Strait Islands. Today only about 25% of Indigenous people live in remote or very remote (R/VR) areas, while most live in urban or semiurban environments. Although the Torres Strait Islands are characterized as very remote, many Torres Strait Islander (TSI) people now live around population centers. **Figure 1** also marks out Australia's states and territories, which were constituted without consideration of distribution of Indigenous people, but now bear most of the responsibility for, and costs of, RRT for their constituent populations.

Table 1 shows the distribution of the 2006 Indigenous population by categories of remoteness of their usual place of residence, and by state/territory (11). New South Wales (NSW) has the largest Indigenous population, but most do not live remotely; Queensland has the next largest Indigenous population but only 19% live R/VR and almost all the Aboriginal people in Victoria and Tasmania live near population centres. However, >80% of Aboriginal people in the Northern Territory (NT) and about 42% in Western Australia (WA) live in R/VR areas.

Assignment of Indigenous status for Australia's census is through self report, and it embraces very heterogeneous populations. Aboriginal people and TSI are distinct groups, of Micronesian and Melanesian descent respectively, with different cultures, lifestyles, diets, body habitus and health status. Moreover, mainland Aboriginal Australians are themselves very heterogeneous in location, languages, non-Indigenous admixture, lifestyle, socioeconomic status, body habitus, health, life expectancy, and access to, and utilization of, services. All documented health parameters, including birth weights, hospitalization rates, and perinatal, infant and adult mortality, are worse in those living in R/VR areas than in those living less remotely.

Cass et al. described vast variation by region and remoteness in the incidence of Indigenous people beginning renal replacement therapy (RRT) from 1993-1998 (12,13) **(Figure 2),** and confirmed it again, 10 years later (14). There was a great, though variable, excess in RRT incidence in Indigenous people in remote and very remote areas, and much lower rates for

those living closer to population centers. The gradient in RRT correlated strongly and directly with level of socioeconomic disadvantage, of which low birth weight is one indicator **(13).** Variation by remoteness has more recently been reported by the Australian Institute of Health and Welfare, from ANZDATA information (15); that report also defined an excess of females among incident R/VR Indigenous people, in contrast with the male excess among non-Indigenous RRT patients (1,15,16).

Figure 3 shows the very different RRT incidence rates by state/territory, ranging from less than twice that of non-Indigenous Australians (about 110 pm per year) to a 14-fold increase (2). These differential rates, which are directly linked to RRT treatment costs on a population basis, largely reflect the different proportions of Indigenous populations by remoteness of residence, as noted in **Table 1.**

Awareness of the excess of kidney disease in Aboriginal people was first heightened in the Top End of the NT and in Central Australia, and renal biopsies were frequently performed to define the processes (17,18). A high frequency of subjectively assessed glomerulomegaly was described, along with mesangial proliferation and focal sclerosis (17,18). Glomerulomegaly was later confirmed by formal measurements, and again shown to associate with focal segmental glomerulosclerosis (FSGS) **(19,20).** However, the definition of some of the morphologic features and their relationships to possible "diagnoses" have been uncertain, and practitioners in other jurisdictions have questioned the applicability of these findings to the Indigenous populations they serve.

We therefore organized a review of all Indigenous renal biopsies across Australia. Its objectives were to reach consensus on pathological findings and terminology, quantify glomerular size, and establish and compare regional biopsy profiles.

Results

Among 1026 biopsies retrieved and reviewed; 735 were from indigenous people. Of these, 38 were of transplanted kidneys, 20 were second or subsequent biopsies of kidneys in the same person and 24 contained no glomeruli or were otherwise non-evaluable. The final Indigenous series consisted of 653 eligible biopsies, whose light microscopic (LM) findings were evaluated by our expert panel of nephropathologists, (**Table 2** and Methods). Photographs or reports of immunofluorescent (IF) examinations were available for 577 and 497 had electron microscopy (EM) studies.

Ten biopsies 10 from Pacific Islanders and 10 of unknown ethnicity, were excluded. There were 249 evaluable non-transplant biopsies on non-Indigenous people, described here; 224 had reports of IF, and 240 had EM photographs and/or reports.

Table 3 shows the number of evaluable biopsies in Indigenous people by state/territory, by categories of remoteness and by Aboriginal, TSI or TSI/Aboriginal designation. Remoteness classification was lacking for 33. Most biopsies were from the NT (Top End and Central Australia) and Queensland, which included all TSI people, with more modest numbers from WA and South Australia, only five ~~for~~ from NSW and none from the Australian Capital Territory. Two Indigenous biopsies were identified in Victoria in 2011, but time did not permit ethics approvals needed for their inclusion in this review. Most Aboriginal biopsies were from people living in R/VR areas, and only 22 were from Aboriginal people living in or near major cities. There were 73 biopsies from TSI people and 12 from people of mixed TSI/Aboriginal descent.

Indigenous biopsy findings were analysed in three groups, Aboriginal R/VR, Aboriginal non-remote (from major cities- MC, inner regional areas- IR, outer regional areas-OR) and as TSI. All were compared with findings in the non-Indigenous biopsies. Data from 11 people of mixed TSI/Aboriginal descent, who had remoteness classification, were included in analyses of both the Aboriginal and TSI groups, which did not substantially change the group results.

Figure 4A shows estimates of the population-based frequencies of biopsies by these categories, using the total number of biopsies as the numerator and the regional 2006 census populations as denominators. This is not an annual estimate because biopsies were gathered from 1982 to 2005, and the Indigenous population has more than doubled over that interval. Nonetheless, with the same assumptions applied to each group, the relative ranking is informative. The figure demonstrates, on an exponential scale, the great excess of biopsies in people from R/VR areas, and a predominance of females in that group, while Aboriginal people closer to population centers had much lower rates and no female excess. Relative to the population-adjusted frequency of biopsies in non-remote Aboriginal people, there was a 6.6-fold greater biopsy frequency in TSI people and a 16.9-fold increase in biopsies from R/VR Aboriginal people. This ranking has similar ranking to that of RRT incidence rates **(Figure 4B).** Rates of overt albuminuria ascertained from limited localized studies in each region (21-24), have similar rankings (**Figure 4C).**

Table 4 shows some demographic and clinical features of biopsy subjects. An excess of females among biopsied R/VR Aboriginal people was confirmed, and was also seen in TSI people. This contrasts with a male excess in less remote-living Aboriginal people, like that in non-Indigenous people. Median age at biopsy was lowest in R/VR Aboriginal people, and in TSI and non-remote Aboriginal people was more like those of non-Indigenous people. Indigenous people were more frequently identified as diabetic at time of biopsy. They more

often had nephrotic range proteinuria, renal insufficiency and renal failure at biopsy than non-Indigenous people.

Table 4 also shows some of the LM morphologic biopsy features. The median number of glomerular profiles per biopsy was about 14. The measured average glomerular tuft volume in non-endstage kidneys was significantly larger in R/VR Aboriginal people than in the other three groups. The values were unchanged when restricted to biopsies with ≥4 glomerular profiles (95% of non-Indigenous and 91% of Indigenous biopsies) **(25).** Almost all Indigenous biopsies had mesangiopathic change (Table2, including items #2,#3) and more often had segmental glomerular tuft sclerosis (items #12-18) than non-Indigenous biopsies. Most biopsies had interstitial inflammation and fibrosis with tubular atrophy and loss (items #23,#24,#28,#29). Crescents, largely cellular and fibrocellular, were present in substantial proportions of biopsies, and involved more than 10% of glomeruli (item #9). Most had vascular changes (items #31-35). Indigenous people more often had end-stage kidneys at biopsy.

The table also shows the final assessments, derived from the experts reviewers' "diagnoses" and the final collation of individual morphologic variables. Leading assessments among R/VR Aboriginal biopsies were diabetic change, mesangiopathic glomerulonephritis (GN) (without IgA) and IgA nephropathy. Indigenous biopsies more often had diabetic changes, with the highest proportions in non-remote living Aborigines and TSI. Nonetheless, diabetic change was found in fewer than half the Indigenous biopsies. The proportion of biopsies with a diagnosis of FSGS was highest in biopsies from R/VR Aboriginal people**.** IgA nephropathy was well represented in all the indigenous groups, although in lower absolute proportions for R/VR Aboriginal people, among whom 14% had crescents. Substantial numbers of Indigenous people had diffuse proliferative GN (40 to 60% with crescents), which included much higher proportions with post-infectious GN. The constitution of the infiltrates associated with interstitial nephritis was similar in all groups: with lymphocytic/histiocytic cells always present, while about 50% also had plasma cells, and about 30% had eosinophils/polymorphonuclear cells. Sixteen Indigenous people, all from R/VR areas had amyloid in their kidney biopsies, which, when (infrequently) specified, was the AL type. The proportions with membranous GN were lower in the R/VR Aboriginal series and the TSI biopsies than in non-Indigenous biopsies. Indigenous people had higher proportions of biopsies with multiple "diagnoses", (excluding cases of secondary FSGS with a specified underlying condition), of which most fell into four major categories—diabetic nephropathy plus post-infectious GN (n=21), diabetic nephropathy plus IgA nephropathy (n=13), diabetic

nephropathy plus interstitial nephritis (n=10) and diabetic nephropathy plus diffuse proliferative GN (n=6).

Figure 5 demonstrates the higher mean glomerular volumes in biopsies of R/VR Aboriginal people compared with the other study groups. **Figure 6** shows that, among groups mutually exclusive groups of 'diagnoses" in non-endstage kidneys in R/VR Aboriginal people, average mean glomerular volumes in decreasing rank order, were mesangiopathic changes alone, FSGS, with similar values for secondary and primary forms (means 4.1, CI 3.5-4.7 vs 3.8, CI 3.1-4.5) and diabetic nephropathy. The average value was also elevated in people with IgA nepropathy without FSGS, but the numbers were smaller.

Table 5 shows that, with retrospective application of the 2010 classification of Thijs et al (26), the major classes of diabetic nephropathy in all subjects groups were severe mesangial expansion (Class IIB) and advanced diabetic sclerosis (Class IV), with substantial proportions with diabetic nodular sclerosis.

Table 6 shows classifications of FSGS **(27).** Cases of secondary FSGS, further defined in the legend of the table, outnumbered apparent primary FSGS in Indigenous people. The major histologic category in both primary and secondary forms was the unspecified type, followed by the perihilar variant.

Applying the proportions of diagnoses/assessment to the relative frequencies of biopsies on a population basis, there was a great excess of most leading biopsy findings among R/VR Aborigines, and a considerable excess in TSI people, as shown in **Figure 7.**

Discussion

This is the first nationwide perspective on renal biopsies in Australian Indigenous people. It shows marked heterogeneity of biopsy rates amongst them, and similarities as well as differences in morphologic findings. Among R/VR Aboriginal people, there was a striking relative and absolute excess of biopsies, a female predominance, a younger age at biopsy and larger glomeruli compared with other Indigenous as well as non-Indigenous biopsies. There was a relative excess of biopsies in TSI people, a female predominance, but with an older age at biopsy. Among the many fewer non-remote Aboriginal people with biopsies, there was no female excess and their ages at biopsy were higher, both more aligned to the non-Indigenous biopsy series.

The biopsy frequencies and gender distributions among the Indigenous groups approximately parallel their RRT rates and patterns. They are also compatible with community-based distribution of overt albuminuria found in a very limited number of localized studies in the relevant groupings, all of which contrast with 0.6% prevalence in adult non-Indigenous Australians, without a female dominance (28). Thus there are reassuring synergies between community-based disease frequency, biopsy rates and terminal renal failure.

The absolute numbers and the population-based rates of biopsies in the states and territories reflect to a large extent the characteristics of their Indigenous populations and the variations of the distributions of their Aboriginal people by remoteness. This helps explain the different impressions of nephrologists in the various states/territories about the frequency and nature of renal disease they see in Indigenous people.

All the usual changes and "diagnoses" were represented in Indigenous people in this biopsy series. Notable in all three Indigenous groups were the high, though variable, proportions of diabetics, more advanced renal disease at biopsy, their higher frequency of diabetic nephropathic changes, of segmental glomerular tuft injury, and of post-infectious GN. Proportions of biopsies with IgA nephropathy, other forms of mesangiopathic GN and membranous GN were not higher in R/VR Aboriginal and TSI biopsies than in non-Indigenous people. However, as we have emphasized **(Figure 7),** wherever the renal disease burden and the biopsy rates are high, the *absolute number* of biopsies with any finding of substantial frequency represents a population-based excess.

We cannot comment on genetic determinants of renal disease among Indigenous people, although genomic studies have begun. However, the major drivers of excess renal disease are potentially modifiable risk factors, such as intrauterine growth retardation and low birth weight, poor nutrition in infancy, childhood and adult life, high levels of adult body mass index (BMI) and diabetes, and the burden of infections and inflammation (**29-31).** These are generally worse in Aborigines from R/VR areas: for example, the frequency of low birth weight is still increased 2-3-fold (32), and, in the NT, was present in about one third of births 40 years ago (30,31,33), when susceptibility was established in current biopsy subjects. Non-remote Indigenous people have higher birth weights, though still about 100 gm short of the non-Indigenous Australian norm, (32) and high levels of diabetes (21), while TSI people have largely normal birth weights (9), but very high levels of adult obesity and diabetes (9, 22).

Our findings support the high frequency of glomerulomegaly previously documented in Aboriginal biopsies from Top End NT (**19)** and extend the observation to other Aborigines in R/VR areas, as described by subjective assessments many years ago **(17).** Specific

proliferative diseases aside, glomerular enlargement is thought to be driven by compensatory hypertrophy in the setting of lower nephron numbers and/or by other hypertrophic stimuli such as overweight or obesity, the metabolic syndrome and diabetes and perhaps inflammation (34). We recently described enlarged glomeruli at autopsy in kidneys of people without obvious renal disease, in the presence of lower nephron number, low birth weight and obesity (34-39). Furthermore, in that autopsy series we found that R/VR Aboriginal people without renal disease had, on average, lower nephron numbers and higher glomerular volumes than regional non-Aboriginal controls, a difference that was probably driven by the lower birth weights of the Aboriginal group (40). We have also described an association of lower birth weights with renal disease in the R/VR community setting (30,31). Thus glomerulomegaly in biopsied R/VR Aboriginal people probably represents compensatory hypertrophy in the presence of congenital nephronopenia related to low birth weight and intrauterine growth restriction, with variable superimposition of postnatal effects of body size, metabolic disorders and infection/inflammation. This is compatible with Brenner's nephropathy of oligonephronia in a multi-determinant or "multihit" model of renal disease in a high risk environment (41,42). Obesity is a less likely to be a primary driver of glomerulomegaly in this setting, for in some R/VR communities rates of overweight and obesity are considerably below those for non-Indigenous Australians (**43,44).** Nephron deficiency is less likely to contribute to glomerulomegaly and renal disease in non-remote Aboriginal people and still less in TSI people, who have higher birthweights, but higher rates of overweight, diabetes and the metabolic syndrome.

The association of glomerular enlargement with FSGS demonstrated in the R/VR Aboriginal groups is also consistent with our previous observation in a smaller number of Top End Aboriginal biopsies (20). Hughson et al have described a similar sequence with FSGS in biopsies of African Americans (45). Glomerular tuft injury might be mediated through deficient podoctye coverage of glomerular basement membrane as glomeruli enlarge, as observed in a model of nephronopenia by Kriz (46), with the largest volumes, demonstrated in biopsies with mesangial change only, representing the earliest phase of injury, and FSGS a more advanced stage. We suggest that glomerular enlargement underlies excessive susceptibility to injury in the presence of other predisposing factors. Glomerulomegaly and its accompaniments will be further addressed in subsequent manuscripts.

Excess renal disease in Indigenous Australians is commonly attributed to type 2 diabetes (2). However, fewer than half the Indigenous biopsy subjects were recorded as diabetic at biopsy, and not all their biopsies showed diabetic change. In fact, among the great excess of biopsies among R/VR Aboriginal people, only one quarter had definitive diabetic change. Although rates of diabetes are high, and many Indigenous people have acquired the diagnosis by age

of 45 years, such a history does not mean that diabetic nephropathy is the primary cause of renal disease in a given patient. This is supported by community-based studies in R/VR Indigenous people that show substantial prevalence of proteinuria in people without diabetes (29,22,21,47), demonstrate that proteinuria/albuminuria appear at higher rates and earlier in life than diabetes (47,48), and predict, often by many years, the later development of diabetes (49). Thus, albuminuria seems to be part of the hemodynamic/ metabolic/ renal syndrome, of which diabetes is a later and variable element. We acknowledge, however, that most diabetic patients with a clinical picture compatible with diabetic nephropathy do not undergo renal biopsies to confirm a diagnosis, and concede that diabetes facilitates and accelerates progression of kidney disease of most causes.

High levels of immune complex and post-infectious disease are compatible with the persistent and recurrent infections and the elevated inflammatory markers in these environments (23,50-53). Excessive accumulation of immune complexes and other deposits and/or their defective clearance could also contribute to, or result from, the mesangiopathy that accompanies glomerular enlargement, at least in the nephron deficiency model (46).

The female excess in renal disease, seen in the RRT population, in community screening programs and now in biopsies in R/VR Aboriginal and TSI people, is not completely understood, although partial explanations might lie in the lower nephron endowment in females (about 17% fewer nephrons (54)), their lower birth weights, higher BMIs and greater central fat deposition, higher rates of diabetes until mid life, and perhaps the effects of pregnancy.

There are many limitations to this study. The consolidation of non-remote Aboriginal people into only one category, obscures potential additional differences. Deficient Indigenous assignment could influence case ascertainment, as well as population denominators. Nephrologists' recall is undoubtedly incomplete, and the designation of "at least half Indigenous" is precarious. There are also variations in renal disease patterns and rates by community, region and state/territory, which were not represented in equal proportions in the series. Furthermore, levels of awareness and ascertainment of preterminal renal disease have varied by region and over time, as have availability of nephrology expertise and philosophies about biopsies. For example, the first spate of biopsies in the Top End of the NT was driven by need to define the lesions. More recently, biopsies have often been limited to people in whom unusual findings might change management, beyond general renal protection and metabolic and blood pressure control. And, as already noted, diabetics with renal disease are usually not biopsied. Nonetheless important patterns are exposed for the first time by this series.

In summary, there are differences in kidney biopsy rates and findings in Australia's Indigenous people. They correlate with similar differentials in ESRD and in mortality. They might be partly explained by differences in stages in the epidemiological and health transitions, in environmental and socioeconomic circumstances, and in genotype and genetic admixture. Due to this variation, predictions and preventative efforts cannot be based solely on the size of the Indigenous population in various regions, states and territories. The greatest absolute reduction in numbers of Indigenous people starting RRT will be achieved through intensive targeting of risk factors in R/VR Aboriginal and in TSI people. Continued improvements in birth weight and reductions in infections promise ultimate reductions in renal disease in those settings, if temporal trends in increase of BMI can be contained.

Methods

All nephrologists in Australia were invited to participate, through identification of Indigenous people who had undergone kidney biopsy, and through participation in biopsy reviews. The major pathology laboratories in each region were likewise requested to identify Indigenous renal biopsies where possible. Ethical review boards at each clinical centre and laboratory, as well as the participating academic centres, and their Indigenous subcommittees, approved the study.

The review was restricted to people considered to be at least half Indigenous. Slides from contemporaneous biopsies on non-Indigenous people were also retrieved in an approximate ratio of one per 3 Indigenous biopsies. Demographic data were derived from hospital databases or biopsy referral forms. Clinical summaries were taken from biopsy referral sheets; the detail was sometimes very deficient.

The expert review group consisted of 5 international nephropathologists (AF, JD, MH, PKS, RS). They, and other interested persons, met for four week-long meetings over a period of three years. A data collection form (Table 2) was developed through a process of progressive modification as findings dictated. The panel, initially blinded to ethnicity, demographic and clinical history of the biopsied subjects, recorded findings on LM review of the slides, and their tentative assessments. The reviews were conducted either in committee, or discussed by the whole committee following review by individual experts. The panel later reviewed their assessments as photographs and reports of IF and EM studies became available. The presence, localization and nature of immune complex deposits were determined and GBMs examined. Finally, diagnoses were refined in the context of an individual's information from all sources, including available clinical data.

In a subsequent phase, glomerular tuft and corpuscle volumes in each biopsy were estimated, as previously described (19), through application of the Weibel and Gomez formula to the average measurement of the areas of all available glomerular profiles on a given section. Later steps included formal measurement of glomerular sclerotic index, interstitial fibrosis and GBM thickness, with techniques and the findings described in later manuscripts.

Statistical analyses were conducted using *Stata Statistical Software: Release 11* (55). Summary data are presented as means with standard deviations or as category percentages. Means were compared using the t-test, accounting for unequal variance as necessary. Proportions were compared using the Chi-squared or the Fisher's exact tests.

Disclosure

The authors have no interests to disclose.

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Table 1. Indigenous Australian population, 2006, by states and territories and remoteness areas, Australian Bureau of Statistics, "Place of Usual Residence"

		Population by categories of remoteness, number/%				
	Indigenous population	Major City	Inner Regional	Outer Regional	Remote	Very Remote
New South Wales	138,057	52.9%	33.5%	18.5%	4.3%	0.8%
Queensland Aboriginal	98,305	32.0%	22.5%	26.5%	9.9%	9.1%
Queensland TSI	18,310	16.3%	13.3%	34.1%	1.5%	34.8%
Western Australia	58,476	35.2%	8.2%	15.0%	15.6%	26.0%
Northern Territory	53,492	-	-	19.5%	22.9%	57.6%
Victoria	30,055	49.2%	35.3%	15.5%	0.1%	-
South Australia	25,469	48.9%	9.2%	23.3%	4.2%	14.5%
Tasmania	16,721	-	53.7%	42.7%	2.4%	1.3%
Australian Capital Territory	3,850	99.8%	0.2%	-	-	-

Source: Adapted from Australian Bureau of Statistics. 2007 (11)

Table 2. Light microscopic data collection items

1 **Number of glomeruli in section:** ☐

2 **Mesangial matrix expansion:**
none / mild / moderate / severe

3 **Mesangial hypercellularity:**
none / mild / moderate / severe

4 **Mesangial interposition:** **no / yes**

5 **Mesangiocapillary change:** **no / yes**

6 **Glomerular deposits:** **no / yes**
epimembranous: no / yes
intramembranous: no / yes
subendothelial: no / yes
mesangium: no / yes
capillary lumen: no / yes

7 **Membranous changes:** **no / yes**
holes / spikes / deposits

8 **Endocapillary proliferation:** **no / yes**
with significant PMNs (>3): no / yes

9 **Crescents:** **no / yes**
in how many glomeruli:
cellular crescents: **no / yes**
in how many glomeruli:
fibrocellular crescents: **no / yes**
in how many glomeruli:
fibrous crescents: **no / yes**
in how many glomeruli:

10 **Glomerulonecrosis:** **no / yes**

11 **Glomerular capillary thrombosis:** **no / yes**

12 **Segmental glomerulosclerosis:** **no / yes**
in how many glomeruli:
with hyalinosis: **no / yes**
in hw many glomeruli:
with foam cells: **no / yes**
in how many glomeruli:

13 **Tip lesions:** **no / yes**
in how many glomeruli:
with foam cells: no / yes

14 **Adhesions:** **no / yes**
in how many glomeruli:

15 **Segmental ischaemic glomerulosclerosis:** **no / yes**
in how many glomeruli:

16 **Indeterminate segmental sclerosis:** **no / yes**
in how many glomeruli:

17 **Perihilar sclerosis/adhesions:** **no / yes**
in how many glomeruli:
with hyalinosis: no / yes

18 **Collapsing lesion:** **no / yes**
in how many glomeruli:

19 **Glomerular solidification:** **no / yes**
in how many glomeruli:

20 **Glomerular obsolescence:** **no / yes**
in how many glomeruli:

21 **Global glomerulosclerosis with hyalinosis:** **no / yes**
in how many glomeruli:

22 **Glomerular infiltration:** **no / yes**
in how many glomeruli:

23 **Interstitial inflammation:**
none / mild / moderate / severe
lympho-histiocytic: no / yes
plasmacytic: no / yes
granulomatous: no / yes
eosinophils: no / yes
PMNs: no / yes

24 **Interstitial fibrosis:** **none / mild / moderate / severe**

25 **Interstitial hemorrhage:** **no / yes**

26 **Periglomerular fibrosis:** **no / yes**
in how many glomeruli:

27 **Fragmentation Bowman's capsule:** **no / yes**
in how many glomeruli:

28 **Tubulitis:** **none / mild / moderate / severe**
PMNs / lymphocytes / eosinophils

29 **Tubular atrophy:** **none / mild / moderate / severe**

30 **Juxtaglomerular apparatus prominent:** **no / yes**

31 **Intimal fibrosis: interlobular arteries:**
none / mild / moderate / severe

32 **Intimal fibrosis: arcuate arteries:**
none / mild / moderate / severe

33 **Arteriolar hyalinosis:**
none / mild / moderate / severe

34 **Hyalinosis of interlobular arteries:**
none / mild / moderate / severe

35 **Fibrinoid necrosis:** **no / yes**
arterioles / interlobular arteries

36 **Arteriolar thrombosis:** **no / yes**

37 **Comment: glomerular size:** **small / normal / large**

38 **Comments:**

39 **Diagnosis:**

1

2

3

Table 3. The number of evaluable Australian Indigenous biopsies by state/territory and remoteness and ethnic group

Indigenous Australians by State/Territory	N	Indigenous Australians by remoteness/ethnic grouping	N
Central Australia	210	Very Remote Aboriginal	86
Top End Northern Territory	143	Remote Aboriginal	65
Queensland	201	Outer Regional Aboriginal	63
Western Australia	54	Inner Regional Aboriginal	3
South Australia	40	Major City Aboriginal	19
New South Wales	5	Torres Strait Islander	73
ACT/Victoria/Tasmania	0	Torres Strait Islander/Aboriginal	12

ACT: Australian Capital Territory

Table 4. Characteristics of persons in the biopsy series and features of their biopsies

	Non-Indigenous	Aboriginal Non-remote*	Torres Strait Islander	Aboriginal Remote/Very Remote	Non-Indigenous vs Indigenous	Aboriginal Remote/Very Remote vs other Indigenous
	N=249	N=92	N=84	N=455	P[Ø]	P[Ø]
Demographic and clinical features						
Female, %	40.2	46.74	56.0	55.4	<0.001	0.337
Age, yr , mean (SD)	45.2 (16.6)	43.3 (14.4)	45.6 (15.8)	39.2 (13.9)[§]	0.0002[Ø]	0.0001[Ø]
Known diabetes, %	14.6	48.3	42.9	42.4	<0.001	0.459
Proteinuria[±], %	67.5	77.5	71.4	85.5	<0.001	0.001
Heavy proteinuria[+], %	22.2	33.7	36.9	43.2	<0.001	0.073
Renal insufficiency[†], %	43.2	59.6	61.9	54.2	0.001	0.144
Renal failure[‡], %	16.6	32.6	33.3	22.5	0.006	0.007
Morphologic features						
Glomerular profiles per biopsy, median (IQR)	15 (10-24)	14 (9-20)	15 (8-23)	14 (8-22)	0.0405	0.5951[Ø]
Mean glomerular volume[Σ], μm^3 x10^6, mean (95% confidence interval)	2.57 (2.4-2.8)	2.54 (2.2-2.9)	2.47 (2.2-2.8)	3.78 (3.6-4.0)	<0.0001[Ø]	<0.0001[Ø]
Mesangiopathic change, %	84.3	94.6	94.1	92.8	<0.001	0.483
Segmental sclerosis, %	45.8	56.5	57.1	63.3	<0.001	0.134
Crescents, %	13.4	18.7	14.8	10.9	0.741	0.046
Percentage of glomeruli per biopsy, with crescents, median (IQR)	16.7 (5.3-46)	16.7 (8.3-28.0)	10.4 (8.0-33.0)	13.8 (8.7-33.3)	0.388[Ø]	0.316[Ø]
Interstitial inflammation/fibrosis, %	88.7	94.4	91.5	91.2	0.167	0.449
Vascular change, %	72.7	81.5	82.1	79.1	0.021	0.449
End stage kidney, %	0.4	4.4	1.2	1.5	0.125	0.330

Assessments/diagnoses[xx]						
Diabetic nephropathy, %	8.4	41.3	48.8	26.6	<0.001	<0.001
Focal segmental glomerulosclerosis, %	16.1	12.0	9.5	19.6	0.707	0.009
Mesangiopathic GN[Ω], %	13.7	6.5	6.0	14.2	0.769	<0.001
IgA nephropathy, %	24.4	19.1	18.2	12.7	0.001	0.067
Diffuse proliferative GN	9.6	12.0	8.3	5.9	0.213	0.060
Post-infectious GN, %	1.6	8.7	11.9	5.9	0.001[Ø]	0.060
Interstitial nephritis, %	9.2	4.4	2.4	4.4	0.003	0.576
Membranoproliferative GN, %	3.6	3.3	3.6	4.0	0.894	0.747
Amyloidosis, %	0.8	0.0	0.0	3.7	0.120[Ø]	0.005[Ø]
Lupus nephritis, %	6.4	5.4	2.4	3.7	0.093	0.887
Hypertensive renal disease, %	4.0	6.5	6.0	2.9	0.883	0.046
Minor change only, %	4.4	0	2.4	2.0	0.022	0.469
Membranous GN , %	6.8	5.4	1.2	1.5	<0.001	0.138
Two or more diagnoses[ɵ], %	5.6	12.0	20.2	9.7	0.009	0.027
Two or more diagnoses[ɵ], major groups[#], %	1.2	7.6	13.1	7.0	<0.001	0.183

*Non-remote: Major city, inner regional and outer regional place of residence
P: T-test/Chi-squared test, [Ø] T-test unequal variance option or Fisher's Exact test, SD: Standard deviation. IQR: Inter-quartile range
GN: glomerulonephritis
[±]Proteinuria: Albumin creatinine ratio ≥34gm/mol or protein creatinine ratio ≥50gm/mol or dipstick protein: ≥1+ or ≥0.15gm/day or ≥0.15gm/L, or stated in history
[+]Heavy proteinuria: Albumin creatinine ratio ≥300gm/mol or urinary protein: dipstick ≥3+ or ≥3gm/day or ≥3gm/L, or stated in history
[†]Renal impairment: S creatinine: >106µmol/L if female or >120µmol/L if male, or stated in history. [‡]Renal failure: S creatinine ≥400µmol/L or stated in history
[Σ]End-stage kidneys excluded
[xx]Additionally: there were 5 cases of reflux nephropathy in remote/very remote Aboriginal (1.1%), as well as rare cases of light chain disease 3 (0.7%), Henoch-Schönlein purpura 0, pyelonephritis 6 (01.3%), thrombotic thrombocytopenic purpura 3 (0.7%) and vasculitis 1 (0.2%), arteriolar nephrosclerosis 20 (4.4%) acute tubular necrosis 1 (0.2%)
[Ω]Mesangiopathic GN, with or without immune complexes but excluding IgA nephropathy or focal segmental glomerulosclerosis,
[ɵ]Two or more assessments/diagnoses. Note: secondary focal segmental glomerulosclerosis not counted as a separate diagnosis.
[#]Two or more diagnoses: Major groups: Diabetic nephropathy and post-infectious GN, diabetic nephropathy and IgA nephropathy, diabetic nephropathy and interstitial nephritis, diabetic nephropathy and diffuse proliferative GN
[§]R/VR Aboriginals were significantly younger than all others biopsied, p<0.0001

Table 5. Diabetic nephropathy classification in the biopsy series (26)

	Diabetic nephropathy classification	Non-Indigenous	Aboriginal Non-remote*	Torres Strait Islander	Aboriginal Remote/Very Remote
Class		N=21	N=38	N=41	N=121
I	Mild or non-specific LM changes and EM-proven GBM thickening	1 (4.8%)	0	0	0
IIA	Mild mesangial expansion	2 (9.5%)	2 (5.3%)	5 (12.2%)	15 (12.4%)
IIB	Severe mesangial expansion	9 (42.9%)	13 (34.2%)	14 (34.2%)	58 (47.9%)
III	Nodular sclerosis (Kimmelstiel-Wilson lesion)	4 (19.1%)	7 (18.4%)	6 (14.6%)	14 (11.6%)
IV	Advanced diabetic glomerular sclerosis	5 (23.8%)	16 (42.1%)	16 (39.0%)	34 (28.1%)

*Non-remote: Major city, inner regional and outer regional place of residence
LM: Light microscopy, EM: Electron microscopy, GBM: Glomerular basement membrane

Table 6. Classification of focal segmental glomerular sclerosis in the biopsy series

Classification and class	Non-Indigenous	Aboriginal Non-remote*	Torres Strait Islander	Aboriginal Remote/Very Remote
Aetiologic				
Primary FSGS	17 (6.8%)	5 (5.4%)	2 (2.4%)	29 (6.4%)
Secondary FSGS	23 (9.2%)	6 (6.5%)	6 (7.1%)	60 (13.2%)
Histologic[+]				
Primary FSGS	*N=17*	*N=5*	*N=2*	*N=29*
Not otherwise specified	14 (82.4%)	5 (100.0%)	2 (100.0%)	15 (51.7%)
Perihilar variant	2 (11.8%)	0	0	12 (41.4%)
Tip variant	1 (5.9%)	0	0	0
Collapsing variant	0	0	0	1 (3.5%)
Cellular variant	0	0	0	1 (3.5%)
Secondary FSGS	*N=23*	*N=6*	*N=6*	*N=60*
Not otherwise specified	13 (56.52%)	5 (83.3%)	4 (66.7%)	38 (63.3%)
Perihilar variant	9 (39.1%)	1 (16.7%)	2 (33.3%)	18 (30.0%)
Tip variant	0	0	0	1 (1.7%)
Collapsing variant	0	0	0	1 (1.7%)
Cellular variant	1 (4.35%)	0	0	2 (3.3%)

FSGS: Focal segmental glomerulosclerosis
*Non-remote: Major city, inner regional and outer regional place of residence
[+]The Columbia classification (27))
An assignment of Secondary FSGS was given if any of the following clinical-pathologic conditions were present; diabetes mellitus, diabetic nephropathy, IgA nephropathy, lupus nephritis, thin membrane nephropathy, immune complex glomerulonephritis, pyelonephritis, reflux nephropathy, familial nephritis or morbid obesity. The remaining biopsies were assigned as Primary FSGS.

Table 7. Clinical correlates of focal segmental glomerular sclerosis (FSGS) in the biopsy series

Correlate, %	Non-Indigenous	Aboriginal Non-remote*	Torres Strait Islander	Aboriginal Remote/Very Remote	Non-Indigenous vs Indigenous	Aboriginal Remote/Very Remote Vs other Indigenous
Primary FSGS	N=17	N=5	N=2	N=29		
Proteinuria[±]	60.0	60.0	100.0	89.7	0.061[Ø]	0.244[Ø]
Heavy proteinuria[+]	40.0	20.0	100.0	51.7	0.554[Ø]	1.00[Ø]
Renal impairment[†]	46.7	60.0	50.0	44.8	0.971	0.684[Ø]
Renal failure[‡]	20.0	0	0	3.5	0.071[Ø]	1.00[Ø]
Secondary FSGS	N=23	N=6	N=6	N=60		
Proteinuria[±]	59.1	83.3	83.3	93.3	0.002[Ø]	0.260[Ø]
Heavy proteinuria[+]	22.7	33.3	0	45.0	0.204[Ø]	0.106[Ø]
Renal impairment[†]	31.8	66.7	16.7	40.0	0.475	1.00[Ø]
Renal failure[‡]	4.6	33.3	0	13.3	0.448[Ø]	0.669[Ø]

[±]Proteinuria: Albumin creatinine ratio ≥34gm/mol or protein creatinine ratio ≥50gm/mol or dipstick protein ≥1+ or ≥0.15gm/day or ≥0.15gm/L, or stated in history
[+]Heavy proteinuria: Albumin creatinine ratio ≥300gm/mol or urinary protein: dipstick ≥3+ or ≥3gm/day or ≥3gm/L, or stated in history
[†]Renal impairment: S creatinine: >106µmol/L if female or >120µmol/L if male, or stated in history; [‡]Renal failure: S creatinine ≥400µmol/L or stated in history
P: Chi-squared test, [Ø] Fisher's Exact test, IQR: Inter-quartile range

Fig 1. Australian Bureau of Statistics' Accessibility/Remoteness Index of Australia (ARIA+)

Source: Australian Bureau of Statistics, 2006 (10)

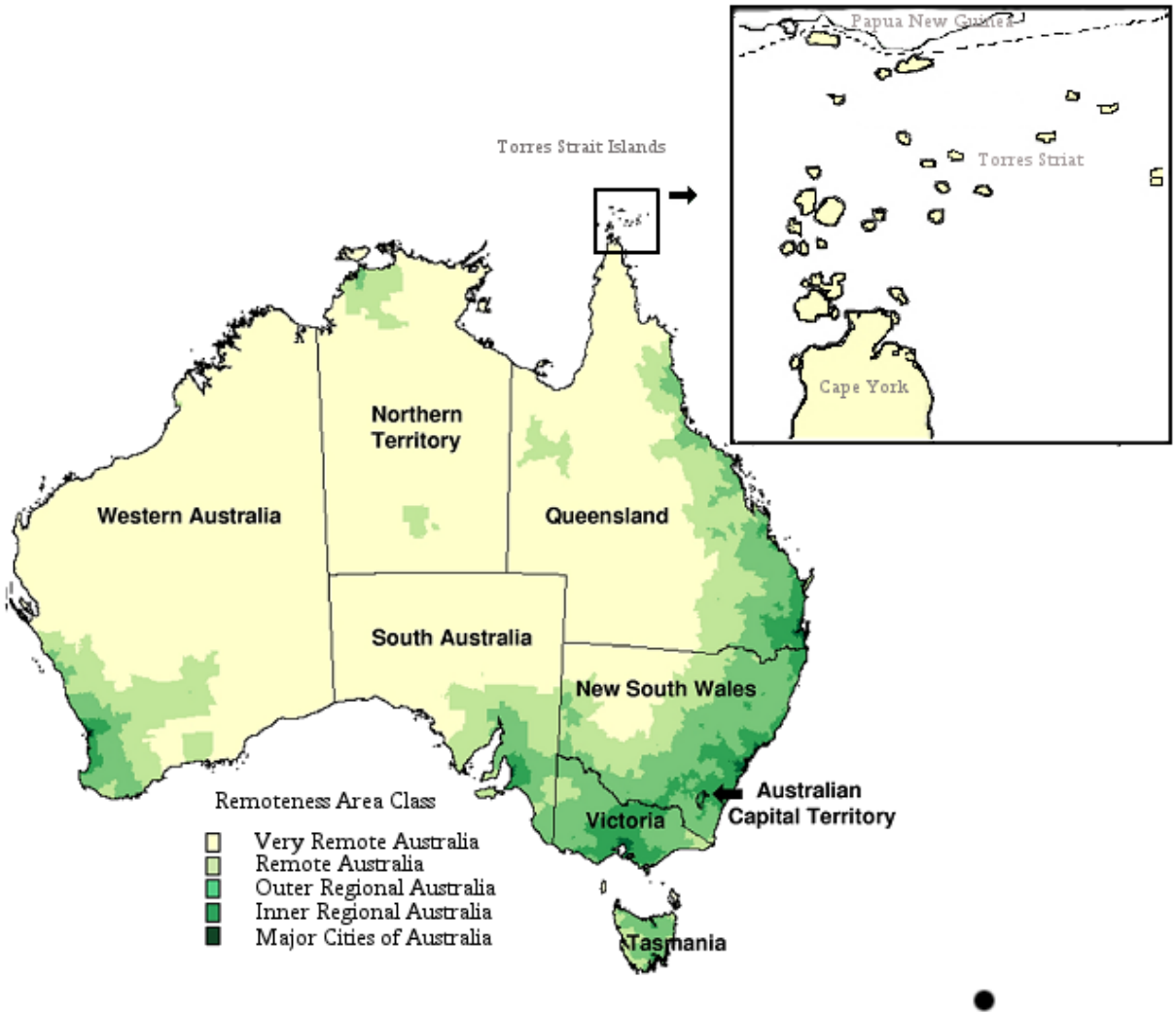

Figure 2. Standardised incidence rates of ESRD resulting in RRT in Indigenous Australians in selected regions, 1993-1998

Note: Standardized incidence ratio

Index population for standardization was the total Australian resident population.

Source: Adapted with permission, Cass et al., 2001(12)

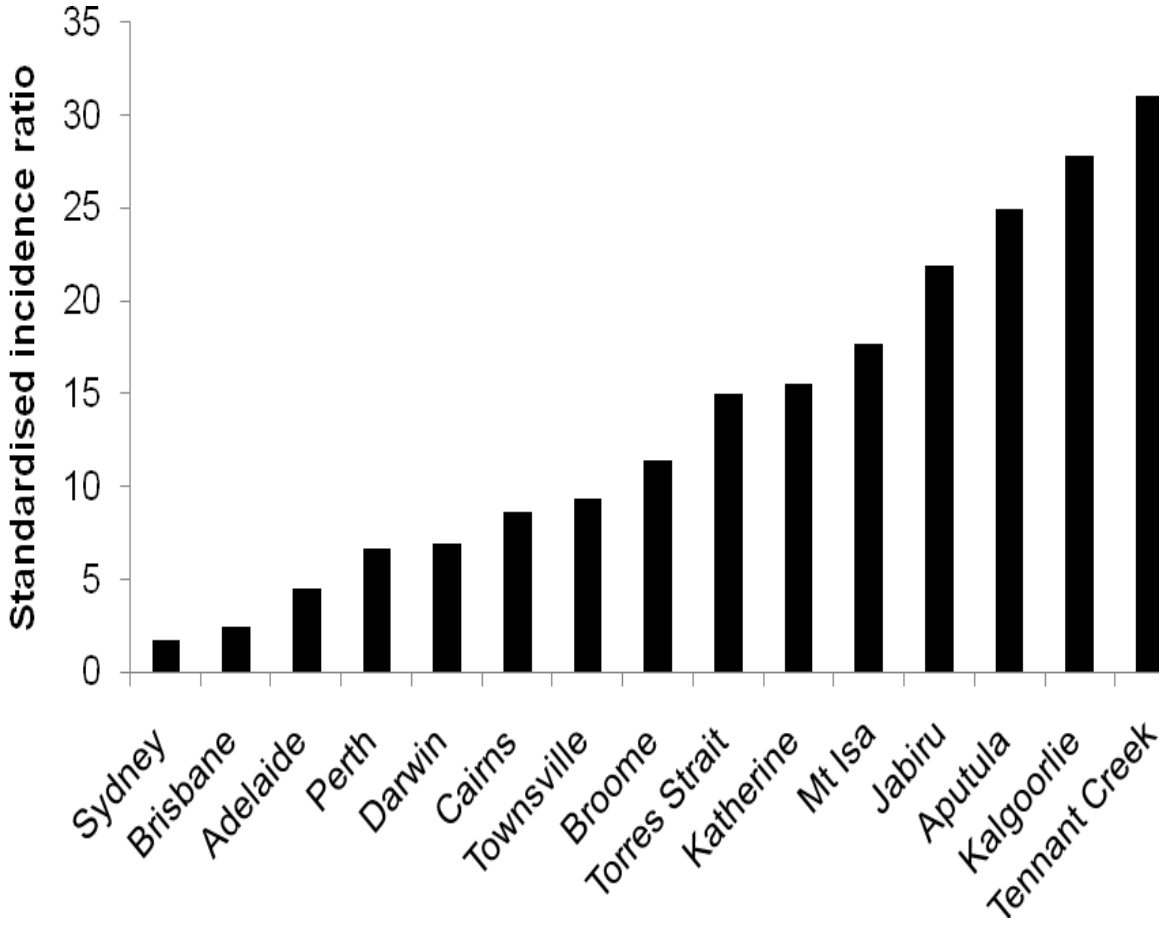

Figure 3. Two year rolling average of annual incidence of ESRD treated by RRT in Indigenous Australians, by state/territory

Notes:

ESRD: End-stage renal disease

RRT: Renal replacement therapy

NSW: New South Wales

ACT: Australian Capital Territory

Source: Adapted from McDonald et al., 2010 (2)

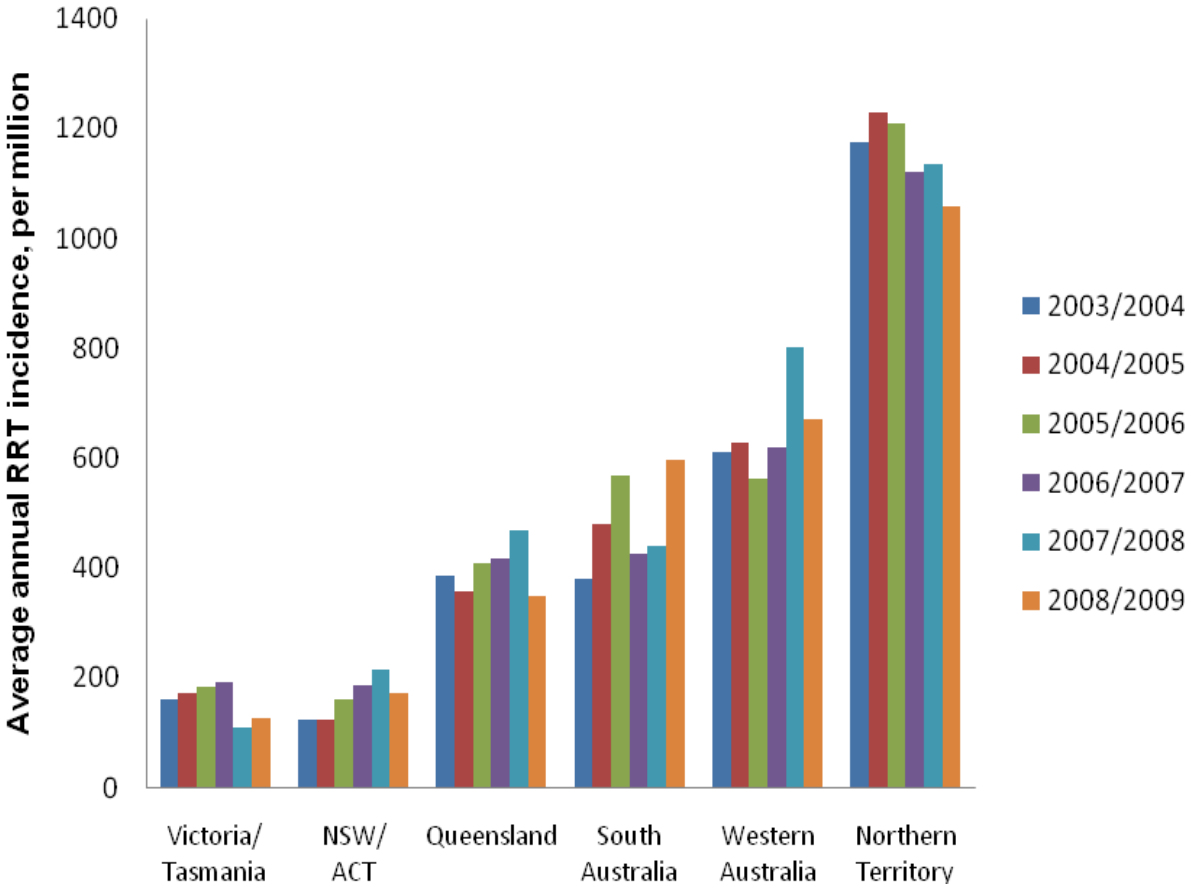

Figure 4.

4a. Biopsy frequency per million persons

4b. Average annual RRT incidence per million persons, 2005-2008

4c. Prevalence of overt albuminuria from community or regional surveys in Australian Indigenous groups

Notes:

RRT: Renal replacement therapy

TSI: Torres Strait Islander

R/VR: Remote or very remote living

Sources:

4a. Denominator: Australian Bureau of Statistics, 2007 (11)

4b. ANZDATA, August 2011 (personal communication) and Australian Bureau of Statistics, 2007 (11)

4c. Darwin: Maple-Brown et al., 2011 (21), TSI: Leonard et al., 2002 (22), Aboriginal R/VR: Derived, using average rates from McDonald et al., 2003 (23) and Rowley et al., (24)

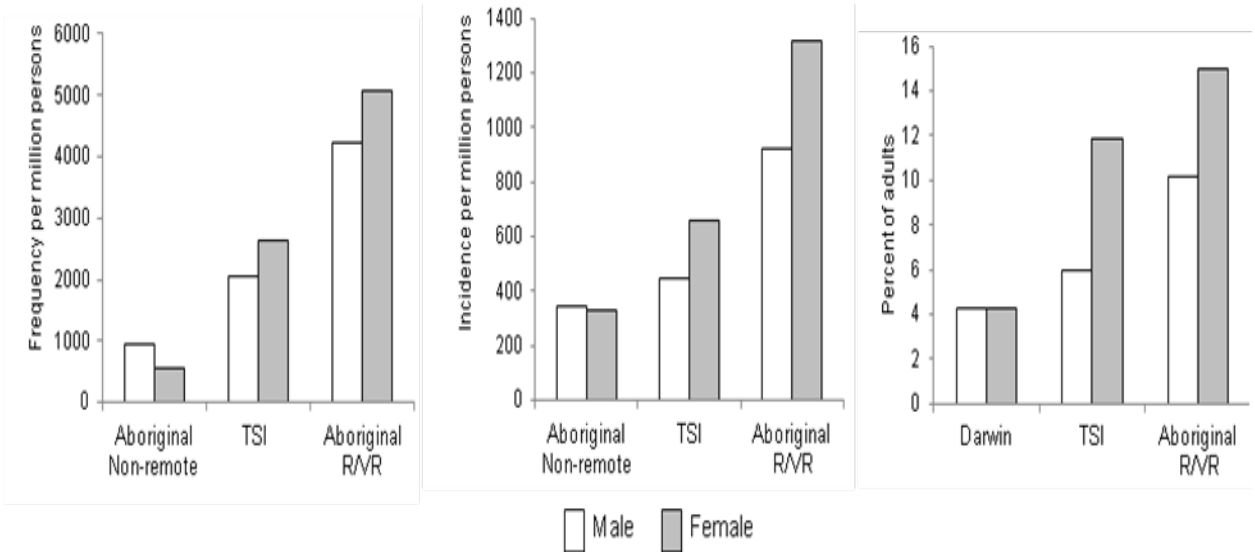

Figure 5. Mean glomerular volume in biopsies of non end-stage kidneys among study groups

Note:

R/VR: Remote or very remote living

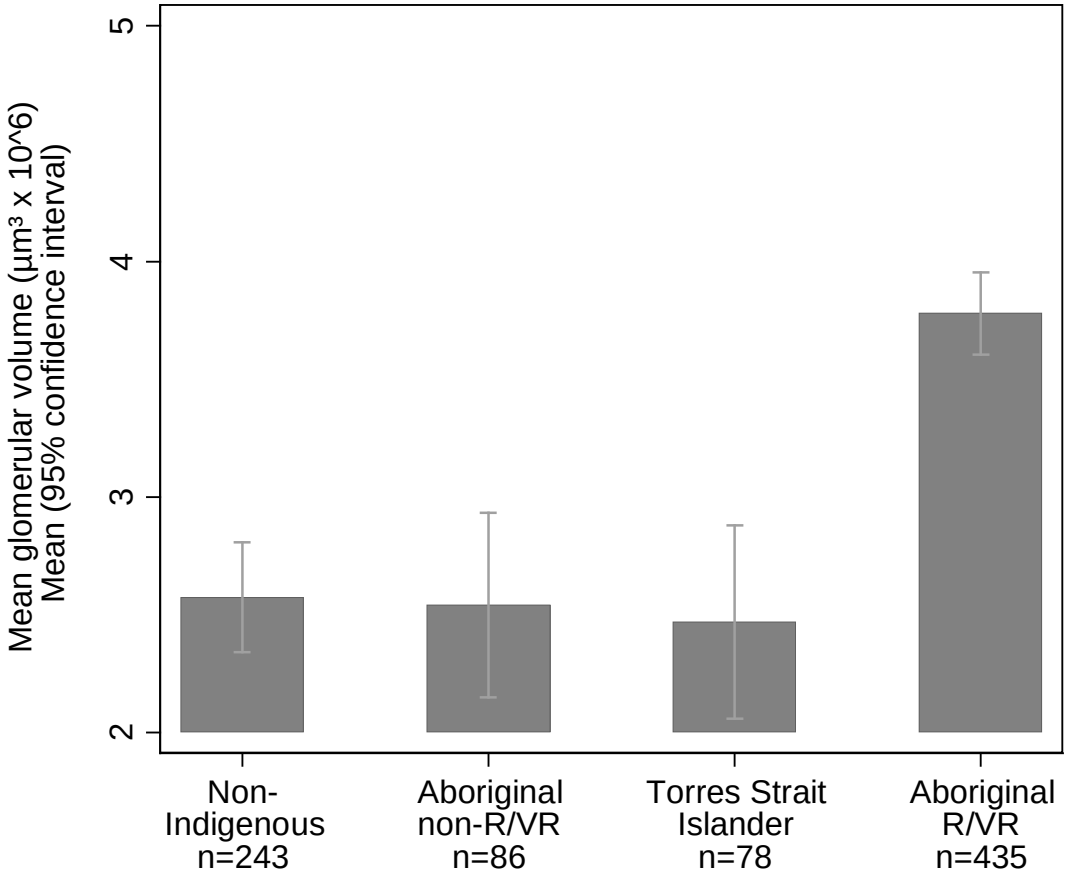

Figure 6. Mean glomerular volume in biopsies of non end-stage kidneys in remote/very remote Aboriginal people by mutually exclusive diagnostic categories

Notes:

FSGS: Focal segmental glomerulosclerosis

GN: Glomerulonephritis

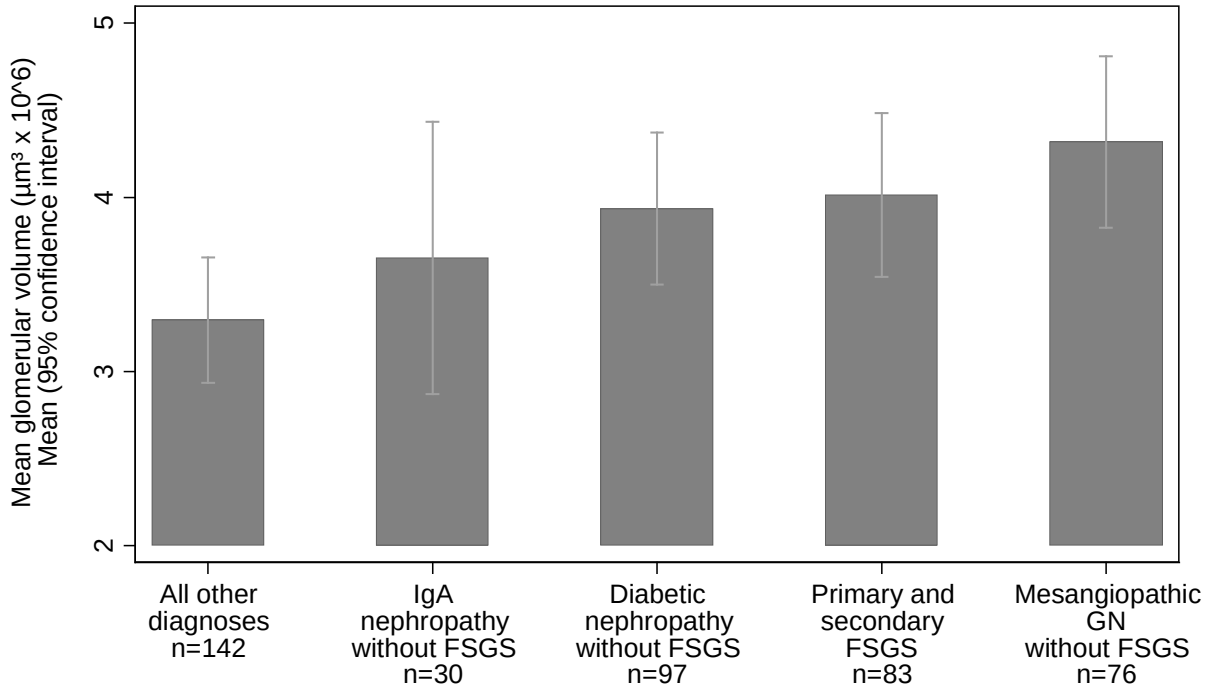

Figure 7. Estimated relative frequency of biopsy assessments per million population

Notes:

TSI: Torres Strait Islander

R/VR: Remote or very remote living

GN: Glomerulonephritis

FSGS: Focal segmental glomerulosclerosis

Source: Denominator, Australian Bureau of Statistics. 2007 (11)