

INTEGRATED MANAGEMENT: CHRONIC KIDNEY DISEASE, DIABETES MELLITUS, HYPERTENSION

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ABSTRACT

The increasing burden of chronic kidney disease and end stage kidney failure presents a challenge for both developed and emerging countries. While dialysis and transplantation consumes an ever-increasing proportion of the health budget in countries such as the United States, Japan and Taiwan, there is limited availability of these expensive therapies in the majority of emerging countries and more so in African nations.

Aims: To review the prevalence, causes and integrated strategies for treatment and prevention of end stage renal disease (ESRD) in Sub-Saharan Africa (SSA).

Materials and Methods: Review of literature and information received from colleagues in Africa.

Results: Approximately 70% of the least developed countries of the world are in SSA. Rapid urbanisation is occurring in many parts of the continent, contributing to overcrowding and poverty. While infections and parasitic diseases are still the leading cause of death in Africa, non-communicable diseases are coming to the forefront. There is a continuing “brain drain” of healthcare workers (physicians and nurses) from Africa to more affluent regions, resulting in large rural areas of Africa having no health professionals to serve these populations. There are no nephrologists in many parts of SSA; the numbers vary from 0.5 per million population (pmp) in Kenya to 0.6 pmp in Nigeria, 0.7 pmp in Sudan and 1.1 pmp in South Africa.

Chronic kidney disease (CKD) affects mainly young adults aged 20-50 years in SSA and is primarily due to hypertension and glomerular diseases. HIV-related chronic kidney disease is assuming increasing prominence and often presents late, with patients requiring dialysis. Diabetes mellitus affects 9.4-million people in Africa. The prevalence of diabetic nephropathy is estimated to be 6-16% in SSA. The current dialysis treatment rate is <20pmp (and nil in many countries of SSA), with in-centre haemodialysis the modality of renal replacement therapy (RRT) for the majority. Transplantation is carried out in a few SSA countries: South Africa, Sudan, Nigeria, Mauritius, Kenya, Ghana and Rwanda, with most of the transplants being living donor transplants, except in South Africa where the majority are from deceased donors. Prevention programmes are in their infancy in most of SSA, due to lack of personnel and resources.

Conclusion: Chronic kidney disease care is especially challenging in SSA, with large numbers of ESRD patients, inadequate facilities and funding, and lack of national or regional registries. Integrated management of CKD and its risk factors is necessary to impact on the burden of ESRD.

Key words: Sub-Saharan Africa – end stage renal disease – chronic kidney disease – renal replacement therapy.

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Chronic kidney disease (CKD) should be viewed as a continuum, ranging from risk factors causing CKD (diabetes

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mellitus, hypertension, glomerular disease) and resulting in the reduction of kidney function, microalbuminuria, macroalbuminuria, end stage renal failure (ESRF) and death¹.

In recent years, major social and demographic changes have taken place in Africa, with large numbers of rural Black populations migrating to the cities, adopting a more western lifestyle, and being exposed to vascular risk factors with respect to diet, smoking habits, and level of physical activity. Recent hospital morbidity and intensive care unit statistics in South Africa indicate that the prevalence of coronary heart disease (CAD) in urban Blacks is increasing².

While the burden of infections presents an enormous challenge in Sub-Saharan Africa (SSA), non-communicable diseases also constitute a major threat to the populations of Africa. This “double burden” poses a public health and economic burden to developing countries. Infections and parasitic diseases are still the leading cause of death in Africa, with over 5.5-million deaths in 2005 and over 2-million deaths due to HIV/AIDS. Non-communicable diseases are coming to the forefront with over 2.4-million deaths in 2005³. While communicable diseases are the leading cause of death in low income countries, chronic diseases such as ischaemic heart disease and stroke feature at number two and four respectively⁴ and were the leading causes of death in South Africa in the previous decade⁵. A more recent study showed that stroke and heart disease were the two leading causes of death in 15-64-year-old Black South African men and women for the period 1999-2006, with death from kidney disease featuring as the fifth leading cause of death in this age group in 2006⁶.

Chronic kidney disease and end stage renal disease

The lack of renal registries means that there are no reliable statistics about the prevalence of chronic kidney disease (CKD) and end stage renal disease (ESRD) in the majority of African countries. Calculations suggest that CKD must be in the range of 200-300 per million of the general population.

Chronic kidney disease is prevalent in Nigeria, accounting for 8-12% of hospital admissions⁷, and affects mainly young adults aged 20-50 years in SSA and is primarily due to hypertension and glomerular diseases. However, in developed countries CKD presents in middle-aged and elderly patients and is predominantly due to diabetes mellitus and hypertension.

Chronic kidney disease has been shown to confer increased risk for cardiovascular (CV) death. The Women's Health Study of $\pm 40,000$ healthcare workers aged >45 y in the United States reported that 1,199 CV events and 856 deaths occurred over 12 years. There were 1,315 women with $eGFR < 60 \text{ ml/min/1.73m}^2$ and an increased risk of CV death with hazard ratio (HR) of 1.68. Average demographics of the study population (age 55, total cholesterol 5.5 mmol/l, HDL cholesterol 1.4mmol/l, not diabetic,

non-smoker, systolic BP 124mmHg) suggested that the increased CV risk was due to a decrease in renal function⁸.

The Framingham study showed increased CV and all cause mortality according to proteinuria status in men and women aged 35-74 years over 16 years of follow up⁹.

Major risk factors for chronic kidney disease in Africa

Hypertension

In the South African Demographic Health Survey of over 13,000 adults, hypertension prevalence was 21.3%, with $<50\%$ treated and $<1/3$ controlled⁵. Hypertension is a leading cause of CKD in SSA ranging from 25% in Senegal, 29.8% in Nigeria, 45.6% in South Africa and 48.7% in Ghana, especially in Black patients¹⁰. Hypertension affects about 25% of the adult population and is the cause of ESRD in 21% of patients on renal replacement therapy in South Africa¹¹. The clinical pattern of hypertension in hospitalised patients takes a rapid course with uraemia and death, frequently from cerebral haemorrhage. Malignant hypertension was an important cause of morbidity and mortality among urban Black South Africans with hypertension accounting for 16% of all hospital admissions¹² and seems to be of lesser frequency in the present era.

Glomerulonephritis

Glomerular disease is common in Africa and is a major cause of ESRD in reports from SSA. Reports from different areas of Africa display differences in the prevalence of patterns of glomerular injury. For example, in Nigerian children with nephrotic syndrome, membranoproliferative patterns on biopsy predominate, whereas in series from South Africa FSGS seems to be commonest^{13,14}. Although epidemiologic data from many areas in Africa is sparse, the incidence of glomerular disease, particularly nephrotic syndrome, seems to be many times higher in Africa. Glomerular disease is more prevalent in Africa and seems to be of a more severe form than that found in western countries, and is characterised by poor response to treatment and progression to renal failure.

One success story is the impact of hepatitis B vaccination in South Africa; prior to the availability of the vaccine, hepatitis B virus (HBV) infections accounted for over 80% of membranous nephropathy in Black children¹⁵. Following vaccination, there were no cases of membranous nephropathy due to HBV reported in the 0-4 year age group¹⁶.

HIV chronic kidney disease

HIV infection is epidemic in SSA. The number of new infections is now declining, with increasing numbers of patients on anti-retroviral therapy¹⁷. Data on the prevalence of HIV-related glomerular disease in Africa is scarce. This relates to the late presentation in Africa of patients with the disease; often patients are dialysis-requiring at presentation. Reported prevalence of CKD in HIV-infected ART-naïve patients in SSA ranges from 6-45% (Table 1)¹⁸. Screening studies in South Africa reported proteinuria in 5.5-6%, with HIV-associated nephropathy (HIVAN) on biopsy in 5-83%¹⁹.²⁰. Recent studies showed that the risk for HIVAN is linked to the MYH9 gene polymorphism, with the risk variant accounting for all or nearly all of the increased risk for FSGS (80%) and HIV-associated collapsing glomerulopathy (100%) that characterise African Americans^{21,22}. The APOL1 variant was reported to be strongly associated with the collapsing glomerulopathy of HIV-associated nephropathy in African Americans²³. An escalating burden of HIV CKD may be anticipated, with increasing life expectancy on ART, ageing of HIV-infected populations and nephrotoxicity of the various drugs used in this population. Following ART, renal function improved²⁴, with renal survival dependent on virological response to therapy²⁵. Lack of response was attributed to a high index of chronic damage in a study of 61 patients with HIVAN presenting with advanced CKD at the time of diagnosis and initiation of ART, 56% of whom reached ESRD in a median time of 4.2 years²⁶. The response of both microalbuminuria (MA) and proteinuria to ART was rapid and sustained, resolving to normal limits within 3-6 months²⁷.

Diabetes mellitus

There are 135-million diabetics worldwide, with a projected increase to 300-million by 2025 and to increase by 170% in developing countries (\pm 40% in developed countries)²⁸. Diabetes mellitus affects 9.4-million people in Africa. The estimated increase in diabetes mellitus in Africa is anticipated to be 12.7-million, an increase of 140%, by 2025. The prevalence of diabetic nephropathy is estimated to be 6-16% in SSA²⁹. Forty percent of diabetics are at risk of overt nephropathy. Diabetic patients with renal disease have a five to six-fold increased mortality rate compared to diabetic patients with no signs of renal disease, or healthy subjects. Cardiovascular risk is increased in diabetics according to the level of proteinuria³⁰ and presence of hypertension.³² Renoprotective strategies have been well-described and include glycaemic control, blood pressure control, anti-proteinuric drugs (rennin angiotensin system blockade and aldosterone antagonists), cessation of smoking, a diet low in salt and saturated fats, exercise and weight control and anti-platelet therapy (Table 2).

Resources for nephrology care

There is a continuing "brain drain" of healthcare workers (physicians and nurses) from Africa to more affluent

regions³², resulting in large rural areas of Africa having no health professionals to serve these populations. Table 3 shows the distribution of physicians and nephrologists in a spectrum of SSA countries and their corresponding rates of renal replacement therapy (RRT). There are no nephrologists in many parts of SSA; the numbers vary from 0.5 pmp in Kenya to 0.6 per million population (pmp) in Nigeria, 0.7 pmp in Sudan, 1.1 pmp in South Africa³³. The United States had 16.7 nephrologists pmp and optimal numbers are 30 nephrologists pmp.

Renal replacement therapy

The availability of RRT is limited in much of Sub-Saharan Africa due to high costs and a shortage of skilled personnel, and is responsible for the high rates of morbidity and mortality. Most dialysis centres are situated in cities, placing a further burden on patients who often have to travel long distances to get treatment. In-centre haemodialysis is the modality of RRT for the majority of African countries. Many patients are under-dialysed; only 20% of patients in a Nigerian centre could afford to have dialysis three times a week, and 70% could only afford it once a week³. As the majority are self-funded, very few are able to sustain chronic dialysis beyond six months.

Renal replacement therapy was accessed by approximately 1.8-million people worldwide in 2004; less than 5% of the dialysis population was from SSA. The current dialysis treatment rate ranges from <20 per million population (pmp) for most of SSA (and nil in many countries of SSA) to 421 pmp in Egypt; the corresponding figures for Japan being 1,940 pmp, USA 1,090 pmp and Germany 800 pmp. Dialysis rates were 45 pmp for haemodialysis (HD) and 23 pmp for CAPD in South Africa; 46 pmp for HD and 3 pmp for CAPD in Sudan and 7.5 pmp for HD and 1.2 pmp for CAPD in Kenya compared to 421 pmp for HD and 0.3 pmp for CAPD in Egypt, 650 pmp for HD and 20 pmp for CAPD in Tunisia³³. Availability of CAPD is limited in Sub-Saharan Africa because of the high cost of dialysis fluids and a perception of a high rate of peritonitis. The average cost of haemodialysis in Africa is \$100 per session. The annual costs of CAPD are equivalent to that of in-centre haemodialysis. Transplantation is carried out in a few SSA countries: South Africa, Sudan, Nigeria, Mauritius, Kenya and Ghana, with most of the transplants being living donor transplants, except in South Africa where deceased donor transplants are carried out to a greater extent (80% deceased donors and 20% living donors respectively). Deceased donation is hampered in many countries by a lack of a legal framework governing brain death, and religious and social constraints. The transplant rate in Africa averages 4 pmp and is 9.2 pmp in South Africa³⁵.

Funding for RRT is primarily private in much of Africa, with the governments of only a few countries providing RRT for small number of patients (e.g. Cameroon, Mali, Mauritius, Rwanda, Sudan, South Africa); indigent South Africans are able to access chronic dialysis at governmental cost only if they are eligible for transplantation. In many African

countries, chronic dialysis is not sustainable, with patients unable to afford dialysis beyond the first 2-3 months.

Strategies for Africa

The above highlights the important facts of chronic disease epidemiology in Africa with tremendous public health ramifications. Hypertension, diabetes, coronary heart disease and ESRD are on the verge of becoming an epidemic in Africa with urbanisation. Treatment for all affected is beyond the reach of most countries in Africa. The only cost effective and sustainable means is prevention. How can Africa prevent or curtail the increasing prevalence of these non-communicable conditions?

Primary prevention strategies

Effective prevention and management of chronic conditions requires a co-ordinated, comprehensive healthcare system involving self-management and regular follow-up. Public education at an early stage – at schools – and on a continual basis, with active media participation to promote healthy living, as well as financial and other incentives, would result ultimately in healthier populations. Countries like South Africa have legislated successfully against smoking in public places.

Immunisation has played an important role in disease prevention. Inclusion of hepatitis B vaccination in the extended programme of immunisation in South Africa in 1995 has impacted on the prevalence of membranous nephropathy due to this aetiology in children.

Secondary prevention strategies

The majority of patients with CKD present with terminal uraemia, requiring emergency dialysis. Screening of high-risk populations for CKD (Table 4) is a strategy that should be implemented, directed at patients with hypertension, diabetes mellitus, proteinuria, HIV infection (Table 5), the elderly, and those with a family history of chronic kidney disease. Simple screening tests such as urinalysis and measurement of serum creatinine, with calculation of GFR are important initial investigations to identify CKD. It is important for different regions to validate formulae for estimating GFR for their populations.

Conclusion

Provision of RRT is especially challenging in SSA. Nephrologists and physicians are faced with large numbers of ESRD patients, inadequate facilities, funding and support. While prevention strategies are recognised as optimal therapy in managing CKD, it is still in its infancy in much of SSA, mainly due to lack of healthcare workers and funding. Prevention of renal disease by early detection of its risk factors, delaying the progression of CKD in those patients

with renal damage and attending to cardiovascular risk factors, as well as timely planning for RRT in those patients reaching ESRD, is essential in the integrated management of CKD and its risk factors, and is necessary to impact on the burden of ESRD.

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Table 1. Prevalence of HIV Chronic Kidney Disease

Sub-Saharan Africa		Global	
Country	Prevalence (%)	Country	Prevalence (%)
South Africa	5.5 - 6	United States	3.5 - 12
Nigeria	38	Europe, Israel, Argentina	3.5 - 4.7
Cote d'Ivoire	26	Hong Kong	18
Tanzania	28.4	Brazil	1.1 - 5.6
Kenya	25	Switzerland	18
Uganda	20 - 48.5	India	27
Zambia	33.5	Iran	20

Table 2. Renoprotection in Diabetes Mellitus

- Glycaemic control: HbA1C<7%
- Blood pressure control <130/80
- Anti-proteinuric agent:
 - RAS blockade (ACEI; ARB)
 - Aldosterone antagonists
- Other measures:
 - Dietary: limit salt and saturated fats
 - Stop smoking
 - Lipid lowering
 - Exercise and weight control
 - Antiplatelet therapy

Table 3. Distribution of Physicians, Nephrologists and Renal Replacement Therapy in Some Sub-Saharan African Countries

Country	Physicians		Neph No PMP	RRT					
	No	Density/10 ⁴		HD	CAPD	TP			
	No		No	No PMP	No PMP	No/year			
Nigeria	34923	3	70	0.6	1000	8	0	70	
Ghana	3240	2	2	0.1	35	2	0	0	
Senegal	594	<1	2	0.2	50	4.2	26	1	0
Sudan	11083	3	25	0.7	1610	46	111	3	74
Kenya	4506	1	15	0.5	260	7.5	30	1.2	10
Rwanda	432	<1	1		0		30	3.7	18
South Africa	34829	8	50	1.1	2070	45	1058	23	240

Abbreviations: No = number; Neph = nephrologists; RRT = renal replacement therapy; HD = haemodialysis; CAPD = continuous ambulatory peritoneal dialysis; TP = transplants; PMP = per million population

Table 4. Screening for Chronic Kidney Disease

- High risk
 - Hypertension
 - Diabetes Mellitus
 - HIV
 - Family history of chronic kidney disease
 - Older age group
- Screening tests
 - Urine: protein creatinine ratio; haematuria
 - Serum creatinine → eGFR

Table 5. Recommendation: Screening for HIV Chronic Kidney Disease

- All patients diagnosed with HIV infection should be screened for proteinuria and kidney function at presentation, and annually if high risk
- High risk for HIV-related nephropathy
 - African descent
 - Low CD4 counts
 - High viral loads
 - Patients with DM, HPT, HCV co-infection
 - 1°/2° relative with ESRD (5.4x increased risk)

Adapted from Gupta et al, Clin Infect Dis, June 2005