

# THE GLOBAL BURDEN OF CHRONIC KIDNEY DISEASE AND THE WAY FORWARD

C. O. Alebiosu, FWACP; O. E. Ayodele, FWACP

**Background:** Chronic kidney disease (CKD) is increasing worldwide at an annual growth rate of 8%. Regional differences exist in the epidemiology of the condition, and non-Whites are more affected.

**Methods:** An English-language literature search using Medline (January 1984–October 2003) was done to assess research/review articles on burden and prevention of CKD. Particular attention was paid to epidemiology and prevention of chronic kidney diseases.

**Results:** The prevalence of CKD is higher in developing countries than in the developed world. The most common causes of CKD in the developing countries are chronic glomerulonephritis and systemic hypertension, diabetic nephropathy being the most common cause in Europe, the United States, and Japan. Factors contributing to the regional differences in the etiology and prevalence of CKD are race and ethnicity, genetic predisposition, increasing prevalence of type 2 diabetes, mortality caused by other disease, obesity, and possibly cigarette smoking. The control of hypertension, dyslipidemia, proteinuria, obesity, avoidance of low birth weight, smoking, and preventing ingesting of heavy metals such as lead are intervention strategies that retard or prevent progression of renal diseases.

The magnitude of the existing burden of illness caused by renal failure, the projections for increasing incidence of CKD, and the limitations of our existing treatments for renal insufficiency all point to the need for clinical and population-based interventions aimed at prevention of CKD.

**Conclusions:** A comprehensive health education campaign and screening of the general populace are needed in order to detect chronic kidney disease early. These measures will ensure appropriate and timely institution of proven measures to halt or reduce progression of CKD. (*Ethn Dis.* 2005;15:418–423)

**Key Words:** Burden, Chronic Kidney Disease, Prevention

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From the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State (COA); Ladoke Akintola University of Technology, Osogbo, Osun State (OEA); Nigeria.

Address correspondence and reprint requests to C. O. Alebiosu, FWACP; Department of Medicine; Olabisi Onabanjo University Teaching Hospital; % P. O. Box 4622, Dugbe Post Office; Ibadan, Oyo State, Nigeria; dralechristo@yahoo.com

## INTRODUCTION

Millions of people around the world suffer from kidney diseases, and these patients will eventually need a form of renal replacement therapy. Hemodialysis, peritoneal dialysis, and kidney transplantation save lives but with great costs, which are becoming a major issue in western countries because they account for a significant proportion of healthcare expenditure.

Chronic kidney disease (CKD) is defined as kidney damage for  $\geq 3$  months and/or glomerular filtration rate (GFR)  $< 60$  mL/min per  $1.73$  m<sup>2</sup> for  $\geq 3$  months with or without kidney damage.<sup>1</sup> Kidney damage is defined as structural or functional abnormalities of the kidney, initially without decreased GFR, which over time can lead to decreased GFR. With time, many patients with chronic kidney disease progress to the stage of chronic renal failure (CRF). Chronic renal failure is defined as either GFR  $< 15$  mL/min per  $1.73$  m<sup>2</sup>, which is accompanied in most cases by signs and symptoms of uremia, or a need for renal replacement therapy to treat complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity.<sup>1</sup> End-stage renal disease (ESRD) is a term used in the United States to refer to a decreasing level GFR accompanied by signs and symptoms of kidney failure that necessitate replacement therapy.<sup>1</sup> Patients treated by dialysis or transplantation, irrespective of the level of GFR, are also categorized as ESRD.

The burden of a disease is quantified by prevalence of the disease in a given population at a particular point in time, mortality rate of the disease, the number of years of life lost due to premature death caused by the disease in a particular year, and the number of years life lived with disability arising from new

cases of the disease.<sup>2</sup> While the first two indicators are easy to calculate, the others are impossible to enumerate without adequate data.

Epidemiologic studies have shown that the incidence of kidney diseases is higher in the developing countries than in the industrialized world.<sup>3</sup> In industrialized countries, the prevalence of CKD increases with age.<sup>4–6</sup> The incidence of CKD is 6–10 times higher in patients between 70 and 90 years of age compared with those between 30 and 50 years. This finding may be a result of the rising prevalence of diseases causing chronic kidney disease such as hypertension and diabetes.<sup>7</sup> In Japan, two thirds of total dialysis patients are  $> 60$  years, and 50% are  $> 65$  years.<sup>7</sup> The vascular and systemic complications in this aging population make these patients not optimal candidates for renal transplantation, and they are less likely to receive a kidney from a living related donor.<sup>7</sup> This trend does not hold for developing countries. For example, in Nigeria, the peak prevalence of CKD is between the third and fifth decade of life, thus contributing to manpower shortage and economic waste.<sup>8–10</sup>

Dialysis and transplantation, while effective, are not optimal therapies for kidney failure. The annual mortality rate of dialysis patients in United States in 1998 was  $> 20\%$ , with cardiovascular disease being the leading cause of death.<sup>11</sup> After adjusting for age, sex, race, and diagnosis of diabetes, mortality from cardiovascular disease is far greater in patients with kidney failure compared to the general population. Among patients treated by dialysis, the risk ranges from 500-fold higher in individuals aged 25–35 years to five-fold higher in individuals aged  $> 85$  years.<sup>12</sup> Expected remaining lifetimes of patients treated by dialysis were far shorter than

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the age-matched general population; these rates vary (depending on sex and race) from 7.1 to 11.5 years for patients aged 40 to 44 and from 2.7 to 3.9 years for patients aged 60 to 64 years.<sup>11</sup> Morbidity of kidney failure is also high, with the mean number of comorbid conditions in dialysis patients being approximately four per patient; the mean number of days spent hospitalized for dialysis patients is 15 per year, and these patients have a far lower self-reported quality of life than that of the general population.<sup>11</sup> Kidney transplant recipients also experience excess mortality despite the preferential selection of patients without cardiovascular disease for transplantation.<sup>1</sup>

In industrialized countries, the costs of dialysis are borne by the government, with only small costs imposed on the patients as copay. Since 1972, the Medicare CKD program has borne 80% of the costs of dialysis and transplantation for approximately 93% of patients in the United States, which allows near universal access to treatment for kidney failure.<sup>1</sup> In Japan, the government pays US\$40,000 to \$50,000 per year to the dialysis provider per patient either on hemodialysis or peritoneal dialysis.<sup>7</sup> The situation in most developing countries is different in that the patient provides the bulk of the fund for renal replacement therapy.<sup>13</sup> This situation makes the treatment unavailable to all patients and also makes long-term dialysis treatment impossible for most patients. In a study in Nigeria, 70.8% of the patients were able to remain on dialysis for less than one month, 12.7% for between

three and six months, 5.1% for between seven and 12 months, and only 1.9% remained on dialysis for more than 12 months.<sup>14</sup>

## THE CURRENT BURDEN OF KIDNEY DISEASES WORLDWIDE

The incidence of end-stage renal failure is increasing worldwide at an annual growth rate of 8%.<sup>15</sup> Data for much of the developing world are often unavailable, but given the prevalence of poor socioeconomic factors, the incidence is likely to be greater.<sup>15</sup>

### Africa

The primary health problems in Africa are HIV/AIDS, tuberculosis, malaria, gastroenteritis, and hypertension, with hypertension affecting about 20% of the adult population.<sup>16</sup> Renal disease, especially glomerular disease, is more prevalent in Africa and seems to be of a more severe form than is found in Western countries.<sup>16</sup> No reliable statistics describe CKD in all African countries. Chronic glomerulonephritis and hypertension are principal causes of CKD in tropical Africa and East Africa, together with diabetes mellitus and obstructive uropathy.<sup>10,16</sup> The availability of dialysis and transplantation is quite variable in Africa but still generally poor. Dialysis and transplant programs in Africa are dependent on the availability of funding and donors. Renal replacement therapy services are still predominantly urban and therefore generally inaccessible to the poorer, less educated rural patient.

Like all other developing countries of the world, no reliable statistics assess the prevalence of kidney diseases in Nigeria. The most common causes of chronic renal diseases in Nigeria are chronic glomerulonephritis, hypertension, diabetes mellitus, and obstructive uropathy.<sup>10</sup> The majority of those with CKD die because of lack of funds, as very few can afford regular maintenance

dialysis.<sup>13,14</sup> Renal transplantation is only recently available but still highly unaffordable to most Nigerians. In Republic of Benin and Togo, nephrologic programs are scarce,<sup>17</sup> and a voluntary nephrologic program was only recently established in one hospital in north Benin and another in south Togo.<sup>17</sup>

In North Africa, the incidence of kidney diseases is much higher than that in West Africa.<sup>18</sup> The principal causes of CKD are interstitial nephritis (14% to 32%), glomerulonephritis (11% to 24%), diabetes (5% to 20%), and nephrosclerosis (5% to 21%).<sup>18</sup> Obstructive/reflux nephropathy, attributed to urinary schistosomiasis, is common in Egypt (7%), Libya, and Southern Algeria.<sup>18</sup> Hemodialysis is the most frequent modality of renal replacement therapy. Peritoneal dialysis is used sporadically. Less than 5% of patients have renal transplantation.<sup>18</sup>

### India, Pakistan, China, and Southeast Asia

In India and Pakistan, no reliable data exist on the prevalence of CKD. Chronic glomerulonephritis is the most common cause, accounting for more than one third of patients, while diabetic nephropathy accounts for about one fourth of all patients in India.<sup>19</sup> Fewer than 10% of all patients receive any kind of renal replacement therapy. Similar to the Nigerian situation, most patients starting hemodialysis die or stop treatment because of cost constraints within the first three months, and fewer than 2% patients are started on peritoneal dialysis. Only about 5% of all patients with CKD end up having a transplant.

In other countries of Southeast Asia, the epidemiology of renal disease in the region is also poorly understood. Chronic kidney disease (CKD) occurs most commonly from chronic glomerulonephritis and nephrolithiasis as well as from complicated acute renal failure due to a variety of stimuli.<sup>20</sup> Many people with chronic renal disease cannot afford the necessary treatment.

Nephrologic work in China started in early 1960s. Both hemodialysis and peritoneal dialysis are widely used in China, with approximately 40% to 50% survival rate in three years.<sup>23</sup> Approximately 5000 patients receive renal transplantation every year.<sup>21</sup> IgA nephropathy is the leading cause of chronic renal disease, among the primary causes of glomerulonephritis, while lupus nephritis is the most prominent among the causes of secondary glomerulopathy.<sup>21</sup> Diabetic nephropathy now constitutes approximately 10% of secondary glomerulopathy.

### **Australia**

Until recently, the Australian Aborigines were experiencing an epidemic of renal and cardiovascular disease. They had a three- to five-fold increase in death rates and a recent annual incidence of CKD of 2760 per million.<sup>22</sup>

### **South American Countries**

In Brazil, chronic glomerulonephritis is the leading cause of CKD.<sup>23</sup> More importantly, renal replacement therapy is accessible to all those in need of it since the government covers most expenses related to replacement.<sup>23</sup>

Although Mexico has the thirteenth largest economy in the world, a large portion of the population is impoverished. Treatment for CKD (estimated at 268 patients per million population) is largely determined by the limited healthcare system and the individual's access to resources. However, Mexico uses proportionately more peritoneal dialysis than other countries of the world, and 80% of peritoneal dialysis consists of chronic ambulatory peritoneal dialysis (CAPD); 1% of patients are on automated peritoneal dialysis, and 19% are on hemodialysis.<sup>24</sup>

### **Western Countries**

In the United States (US), concern exists about the steady growth in the numbers of patients who require dialysis and associated healthcare costs.<sup>25</sup> In

1972, the population of patients receiving maintenance dialysis was approximately 10,000. The average cost of providing care for a patient receiving dialysis is \$45,000 per year. In 1995, inpatient and out-patient expenditures for CKD, including hemodialysis, peritoneal dialysis, and transplantation, totaled \$13.1 billion, with 75% of this cost borne by the federal government. In the 1999 annual report of the United States Renal Data System, more than 300,000 patients with CKD were receiving dialysis. By 2010, approximately 520,000 patients will be receiving maintenance dialysis, and CKD-related medical expenses are estimated to total more than \$28 billion.<sup>25</sup> Annual healthcare costs are nearly 10 times as high for a patient with CKD as for the average Medicare beneficiary. Similar to the situation in Europe and Japan, diabetes mellitus is the most common cause of chronic renal failure in the United States.

Diabetes mellitus was the underlying cause of renal failure in 23% of Canadian patients seen between January 1981 and December 31, 1996.<sup>26</sup> The mean annual ESRD prevalence is projected to increase by 5.8% during 1997–2005, which would result in 32,952 Canadians requiring RRT by the end of 2005.<sup>26</sup> This figure represents a relative increase of 85% over the prevalence in 1996.<sup>26</sup>

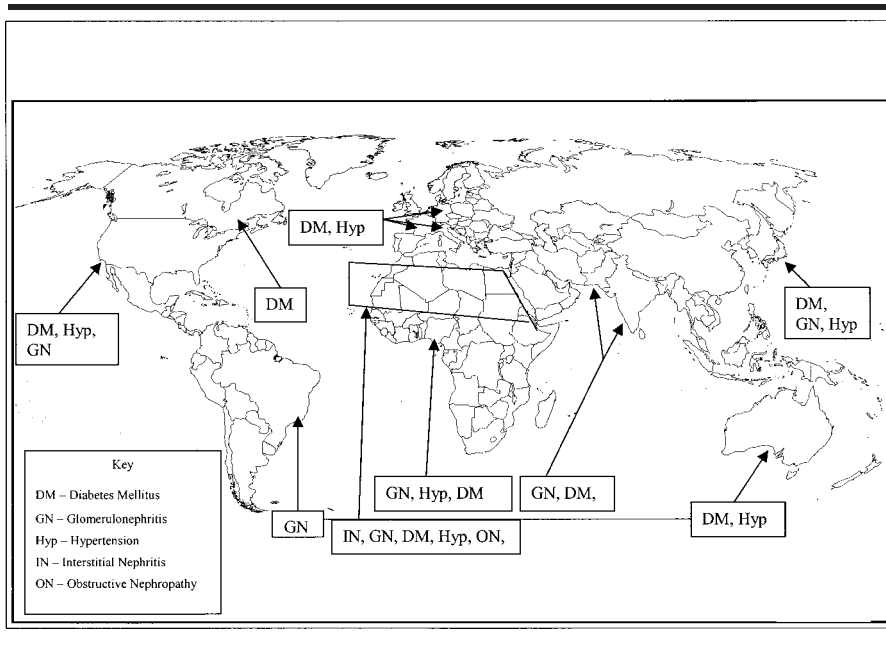
## **REGIONAL DIFFERENCES IN THE ETIOLOGY AND PREVALENCE OF CHRONIC KIDNEY DISEASE**

Factors contributing to the regional differences in the etiology and prevalence of CKD include race and ethnicity, genetic predisposition, increasing prevalence of type 2 diabetes, competing mortality, obesity, and possibly cigarette smoking. Epidemiologic studies have shown that African Americans, American Indians or Alaska Natives, and His-

panics have higher prevalence of CKD compared to Whites. Even after adjusting for confounding factors such as lower socioeconomic status and increased incidence of hypertension in Blacks, a 4.8-fold greater risk of ESRD exists in Blacks compared to Whites.<sup>27</sup> The rates of new cases of ESRD are four times higher in African Americans or Alaska Natives and 1.5 times higher in Asians or Pacific Islanders than in Whites.<sup>27</sup>

Diabetes has become the leading cause of ESRD in many countries of Western Europe, the United States, and Japan (see Figure 1). In the United States, the proportion of patients with diabetes as the cause of ESRD increased from 27% in 1988 to 36% in 1992 and 40% in 1995.<sup>28</sup> The reasons for this trend include increase in the prevalence of diabetes in the population, improvement in survival of patients with type 2 diabetes, and increasing acceptance of elderly polymorbid patients into renal replacement programs. A similar trend of increasing prevalence of diabetes as a cause of ESRD has also been reported from Nigeria.<sup>29</sup>

The increasing prevalence of diabetes in most populations is partly due to increase in the prevalence of obesity. Currently, more than one billion adults are overweight, with at least 300 million of them clinically obese.<sup>30</sup> The rates of obesity have risen three-fold or more since 1980 in some areas of North America, the United Kingdom, Eastern Europe, the Middle East, the Pacific Islands, Australia, Southeast Asia, and China.<sup>30</sup> Similar increase in obesity prevalence is also noticed in the developing countries.<sup>30</sup> More worrisome is the increasing epidemic of childhood obesity with increasing diagnosis of type 2 diabetes in children.<sup>30</sup> The increasing prevalence of type 2 diabetes in adults and children will in turn increase the prevalence of diabetic ESRD. Obesity is also associated with focal and segmental glomerulosclerosis (FSG).<sup>31</sup> The long-term prognosis of obese patients with biopsy-proven FSG is poor, with one



**Fig 1. Common causes of CKD by regions**

half ultimately developing advanced renal failure.<sup>31</sup> Furthermore, obesity is associated with an enhanced risk of chronic graft dysfunction after renal transplantation<sup>32</sup> and progression of renal disease in IgA nephropathy.<sup>33</sup> Glomerulonephritis also remains one of the leading causes of CKD in tropical Africa as a result of various infectious agents (see Figure 1).<sup>34</sup>

Another factor responsible for the regional differences in the prevalence of ESRD is competing mortality. The life expectancies at birth of males and females in sub-Saharan Africa are 48.4 and 50.1 years compared to 73.4 and 80.5 years, respectively, for established market economies.<sup>35</sup> Non-communicable diseases, maternal, perinatal, and nutritional disorders accounted for 65% of all deaths in sub-Saharan Africa, with 53% of all deaths occurring between ages 0 and 4 years.<sup>35</sup> This low life expectancy precludes many people from developing diabetes and diabetes-related ESRD since prevalence of diabetes increases with age. For the industrialized countries, the vast improvements in treatment and reduction in deaths from acute complications of diabetes, ampu-

tations, or coronary heart disease have resulted in improved survival with concomitantly higher risk of developing diabetes-related ESRD.<sup>26</sup>

The regional difference in smoking prevalence could also have contributed to the regional differences in prevalence of CKD. Smoking prevalence is said to be highest in East Asia, the Pacific, Europe, and Central Asia and lowest in sub-Saharan Africa.<sup>36</sup> Smoking increases the risk of developing microalbuminuria, shortens the interval from microalbuminuria to overt nephropathy, and accelerates progression of nephropathy and loss of glomerular filtration rate.<sup>37-39</sup>

### PREVENTION OF CHRONIC KIDNEY DISEASES—THE WAY FORWARD

The magnitude of the existing burden of illness caused by renal failure, the projections for increasing incidence of CKD, and the limitations of our existing treatments for renal insufficiency all point to the need for clinical and population-based interventions aimed at prevention of CKD.<sup>40</sup>

The adverse outcomes of CKD can be prevented or delayed through interventions in the earlier stages of the disease, which can be detected through laboratory testing such as measurement of serum creatinine, estimation of GFR, measurement of urinary albumin excretion, urine microscopy for cellular elements and casts, and by radiologic investigations.<sup>1</sup> The therapeutic interventions that have proven effective include strict blood sugar control in diabetes, strict blood pressure (BP) control, use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) and protein restriction.<sup>41</sup> Unfortunately, CKD is underdiagnosed and undertreated in the developed and industrialized countries, which leads to lost opportunities for prevention of complications and worst outcomes for patients with CKD.<sup>1</sup> For example, analysis of data from NHANES III on the adequacy of drug treatment of hypertension in patients with elevated serum creatinine shows that only 11% had their BP reduced to <130/85 mm Hg<sup>42</sup> the level recommended to slow the progression of CKD.<sup>43</sup> Also, only 27% had their BP reduced to <140/90 mm Hg, the level recommended to prevent cardiovascular disease in individuals without pre-existing target organ damage.<sup>41</sup> In addition, various studies in developing and industrialized countries have also shown adequate BP control in only 25% to 50.3% of the patients.<sup>44-47</sup> Hospital records from Medicare beneficiaries in Georgia analyzed for adequacy of diagnosis and ACE inhibitor treatment of diabetic and hypertensive kidney disease showed that neither diabetic nor hypertensive patients, who were at increased risk for CKD were adequately evaluated or treated with proven agents.<sup>48</sup>

We must also do a better job of implementing what we already know.<sup>40</sup> The fact that population surveys consistently identify a low level of awareness and undertreatment of major, modifiable risk factors for renal disease is a bad

reflection of the effectiveness of the clinical and public health communities.<sup>40,49</sup> Solutions to these problems will include increasing the general public's awareness of the importance of CKD risk factor detection and treatment and increasing the availability of cost-effective programs for prevention and treatment of renal disease risk factors. These solutions will involve targeted screening such as urine examination, BP check, and plasma glucose estimation. Such targeted screening will help in identifying persons at risk for developing CKD and in diagnosing early disease so that appropriate and effective interventions can be instituted. Such targeted screening had been done in Bolivia,<sup>3</sup> Benin,<sup>17</sup> Togo,<sup>17</sup> Australia,<sup>50</sup> Singapore,<sup>51</sup> and the United States.<sup>52</sup> In addition, patients with hypertension and diabetes should have strict BP and sugar control. Also, use of skin-lightening creams, indiscriminate ingestion of drugs, and ingestion of herbs that are not approved by drug regulatory bodies should be discouraged.<sup>49,53</sup>

Chronic renal failure patients are referred late to nephrologists in both developing and industrialized countries around the world.<sup>9,54-56</sup> Early referral to a nephrologist will ensure institution of measures to slow the progression of chronic renal disease; timely and proactive development of vascular access required for hemodialysis; and optimization of hematologic, endocrine, nutritional, metabolic, and hemodynamic function in the face of progressive renal failure.<sup>44</sup> Chronic renal failure patients should be referred early to nephrologists when the estimated creatinine clearance is <29 ml/min (stage 4 of CKD).<sup>1</sup>

Factors that have been shown to increase the risk of progression of renal diseases include hypertension, dyslipidemia, underlying nephropathy, high dietary protein intake, and proteinuria. Others are smoking, hyperglycemia, low birth weight, obesity, metabolic syndrome, genetic factors such as angiotensin converting enzyme 'DD' genotype

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*Early referral to a nephrologist will ensure institution of measures to slow the progression of chronic renal disease . . .*

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and chromosome 1q21, and exposure to lead.<sup>27</sup> The control of hypertension, dyslipidemia, proteinuria, and obesity and avoiding low birth weight, smoking, and heavy metals such as lead are intervention strategies that will retard or prevent progression of renal diseases.<sup>41</sup>

Finally, in order to succeed in our bid to prevent CKD, collaboration and cooperation must exist between health professionals, professional societies, government agencies, lay organizations, and the pharmaceutical industry as well as recognition that the CKD epidemic is a worldwide phenomenon that demands an international collaborative response.<sup>40</sup> Given sufficient commitment to implementation of existing knowledge and a concurrent, continued dedication to acquiring new information, much of the suffering from CKD can be expected to be reduced and eliminated during the course of the next two to three decades.<sup>40</sup>

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**AUTHOR CONTRIBUTIONS**

*Design and concept of study:* Alebiosu, Ayodele  
*Acquisition of data:* Alebiosu, Ayodele  
*Data analysis and interpretation:* Alebiosu  
*Manuscript draft:* Alebiosu, Ayodele  
*Statistical expertise:* Alebiosu  
*Administrative, technical, or material assistance:* Alebiosu, Ayodele  
*Supervision:* Alebiosu