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Diabetic Kidney Disease in Africa: Epidemiology, Management, and Prevention

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ABSTRACT

Diabetes is a worldwide pandemic, with more than 75 percent of people with diabetes estimated to live in developing nations by 2025. This epidemic in developing countries has been attributed to urbanization and westernization, altered nutritional intake, increasing sedentary lifestyle, and established risk factors, including age, and gender. The management of diabetic kidney disease follows a multi-disciplinary approach, with blood glucose control, hypertension control, pharmacologic intervention, and lifestyle modification such as weight reduction and increased physical activity. In most of Sub-Saharan Africa, economic challenges pose a barrier to treating and preventing diabetes and its complications. This is due to a lack of screening, the rising cost of medications, and inadequate universal health coverage such as national insurance schemes, resulting in affected individuals seeking treatment late.

This article elaborates on the risk factors, epidemiology, and treatment strategies of diabetic kidney disease and highlights strategies for its prevention in Africa.

KEYWORDS: *Diabetes, Diabetic Kidney Disease, Africa*

INTRODUCTION

For centuries, communicable diseases and uncontrolled epidemics were the major cause of death worldwide. However, breakthroughs in medicine and research have curbed the deleterious effects of communicable diseases on society. In its stead, non-communicable diseases are at the forefront of mortality.[1] The World Health Organization (WHO) estimates that non-communicable diseases, including cardiovascular diseases, diabetes, cancers, and obesity-related conditions, account for 59% of global deaths worldwide and almost half (49.5%) of the global disease burden.[2]

Diabetes is a worldwide pandemic, with more than 75 percent of people with diabetes estimated to live in developing nations by 2025. (Table 1) Poorly managed diabetes results in severe complications, including end-stage renal failure, blindness, amputation, and cardiovascular diseases [3], that burden developing countries with limited resources, who still struggle to meet the challenges of infectious diseases.[2]

Most cases of diabetes fall into one of two categories: Type 1, which is caused by severe insulin deficiency, occurs in <10% of all cases and tends to occur in younger subjects. Type 2 diabetes is usually seen in older adults but is diagnosed with increasing frequency in younger age groups. Insulin resistance and islet beta cell defect are the characteristic pathologic findings in type 2 diabetes.[3]

Diabetes is the most common cause of chronic kidney disease (CKD) in developed countries and a major cause in developing countries.[4] Other predisposing factors to CKD include hyperglycemia, systemic hypertension, glomerular hyperfiltration, low nephron mass, genetic predisposition, proteinuria, lipid abnormalities, and Advanced Glycosylation End Products (AGEs).

Diabetic kidney disease (DKD) is a heterogeneous clinical condition characterized by the presence of persistent overt proteinuria (urine albumin creatinine ratio or UACR ≥ 300 mg/g or 3 mg/mmol) and declining renal function reflected by an estimated glomerular filtration rate (e-GFR) of < 60 ml/min/1.73 m^2.[5]

Diabetic kidney disease (DKD) is a complication in 20-40% of all people with diabetes.[6] It is a chronic complication of both type I diabetes mellitus (DM) and type 2 DM [6]; however,

diabetic kidney disease is a more common complication of type-2 diabetes than in type-1 diabetes.[7] Since type-2 diabetes accounts for >90% of all diabetes cases worldwide, the current diabetes epidemic is attributable predominantly to rising cases of type-2 diabetes [3], which in turn is largely related to the increase in obesity.[8]

Table 1: Features of type-2 Diabetes by region

	Developed Countries	Developing Countries
Number of cases (1995)	51 million	84 million
Projected cases (2025)	72 million	228 million
Rate of increase	Male > Female	Female > Male
Peak Age	>65 years	45 – 64 years

**Data from King H. Aubert RE. Herman WH. 1998.[6]*

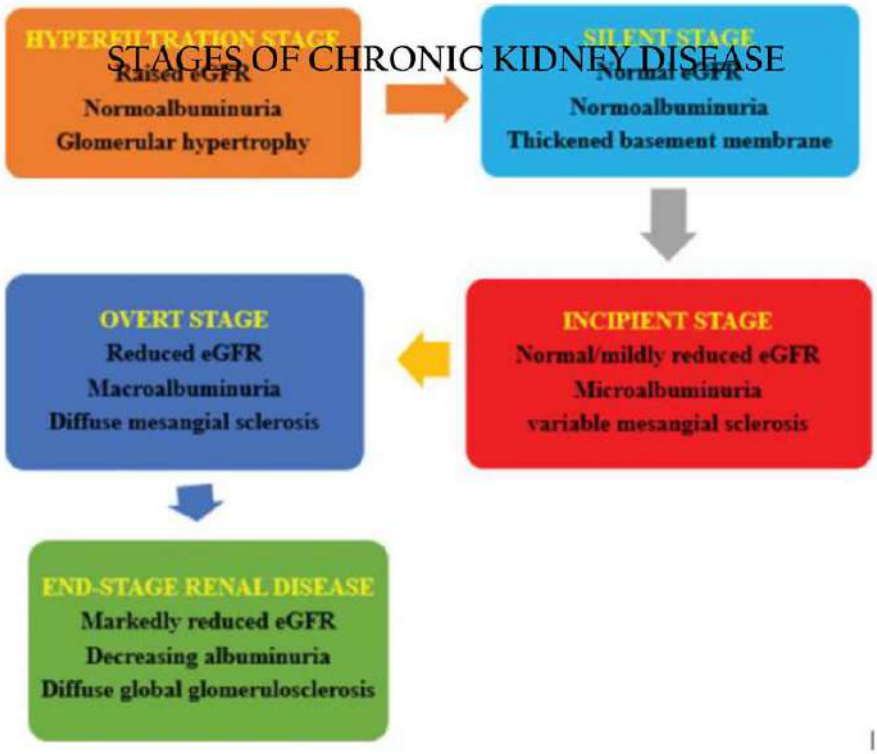
PATHOGENESIS

The pathophysiology of DKD involves four pathways: metabolic, hemodynamic, inflammatory, and fibrotic.[10] These pathways are often disrupted in diabetes mellitus, leading to the functional, biochemical, and structural changes seen in DKD.[11]

1. **Metabolic pathway**: this is mediated by increased oxidative stress, formation of advanced glycation end products, and increased glucose flux through the hexosamine pathway, thereby generating a higher level of transforming growth factor-β.[12]
2. **Hemodynamic pathway**: activating the renin-angiotensin-aldosterone system (RAAS), elaborating nitric oxide, and the secretion and activation of endothelin.
3. **Inflammatory pathway**: There is increased production of transforming growth factor-α and enhanced synthesis of serum amyloid A.
4. **Fibrotic pathway**: this is facilitated by transforming growth factor-β, vascular endothelial growth factor, and connective tissue growth factor.

EPIDEMIOLOGY

The number of individuals diagnosed with diabetic kidney disease has increased steeply over the years, alongside the diabetes epidemic.[7] Type 1 diabetes is predominantly a disease of persons of European ancestry. It is much less prevalent among persons of African, Asia, and other non-European descent, whereas type 2 diabetes is disproportionately more prevalent in non-European than European populations.[3]



Some unique aspects of the diabetic epidemic in developing nations include age, gender, and urbanization. In developing countries, the greater proportion of people living with diabetes is in the younger age group, 45-64, compared to those aged >65 in developed countries. Furthermore, in developed countries, more men are affected with diabetes than women, whereas the gender ratios are reversed in developing countries. This combination of younger age and female predisposition increases the likelihood of intrauterine fetal exposure to diabetes in developing countries and increases the risk of developing future metabolic disorders.[3]

Diabetic kidney disease is uncommon if diabetes is less than one-decade duration and there is marked racial/ethnic and international difference in the epidemiology of Diabetic Kidney Disease. The prevalence of diabetes, especially type 2, affects approximately 13% of African Americans, 9.5 of Hispanics, and 15% of Native Americans, and the incidence of diabetic kidney disease is shown to be multiple times higher in Blacks than in Whites. However, the prevalence of any chronic kidney disease, especially DKD, is significantly higher in citizens of Asian origin, presumably because of different genetics and a lack of awareness of kidney complications of diabetes.[6]

In Sub-Saharan Africa, Nigeria has the highest number of individuals living with diabetes mellitus. In Nigeria, the third most common cause of chronic kidney disease is diabetes mellitus, after hypertension and chronic glomerulonephritis. However, diabetes remains the most common cause of end-stage renal disease globally.[11]

RISK FACTORS

Risk factors for diabetic kidney disease (DKD) are broadly classified as modifiable and non-modifiable. *Non-modifiable risk factors* include genetics, family history of type II diabetes or DKD, gender, older age, and ethnicity (Black, Hispanic, American, Indian). *Modifiable risk factors* include poor glycemic control, obesity, hypertension, high salt intake, sedentary lifestyle, and dyslipidemia.[13]

The worldwide incidence of diabetes has increased significantly over the past two decades, attributable to the obesity epidemic that has simultaneously occurred.[13] In Africa, this has been attributed to urbanization and modernization of cultures. The nutritional intake change combined with increasingly sedentary lifestyles also contributes to the emergence of diabetes as a major new health threat worldwide.[2,14] In addition, in most African countries, obesity is considered a sign of luxury and a sign of high socio-economic standing.[15] A study on dietary patterns in urban Ghana showed that high-fiber diets such as fruits and vegetables were associated with a reduced risk of type 2 DM.[16] Furthermore, in most African countries, fruits and vegetables are available seasonally and are not incorporated into daily feeding.[17]

The rapid urbanization of African countries has resulted in decreased physical activity. Driving and access to technological devices have largely displaced the physical activity usually obtained from manual labor.[17] There are many other implicated cases of CKD in sub-Saharan Africa, including the widespread use of herbal or traditional medicine. Up to 80% of the populations in sub-Saharan countries are estimated to use herbal or tribal medicines, which are thought to have been associated with 35% of all new cases of acute kidney injury.[18]

Economic challenges to preventive care in most low-middle-income countries include a lack of sufficient national health coverage and a high cost of medical care.[13] This results in affected individuals seeking treatment late and presenting with severe complications, including nephropathy and gangrenous foot ulcers. In most of Sub-Saharan Africa, renal replacement therapy (either chronic dialysis or transplantation services), laser surgery for retinopathy, and invasive cardiology procedures are not routinely available, even in tertiary care institutions.[3] By 2030, more than 70% of patients with End Stage Renal Disease (ESRD) are estimated to be living in low- and middle-income countries (LMICs) such as those in sub-Saharan Africa. This estimation is alarming since the global prevalence of maintenance dialysis has doubled since 1990, and renal replacement therapy was accessed by 1.8 million people worldwide in 2004, with less than 5% of that population coming from sub-Saharan Africa.[18]

TREATMENT

Diabetic Kidney Disease (DKD) has been identified as the major cause of End Stage Kidney Disease in diabetic patients. However, because the pathogenesis is not fully understood, the treatment modalities are the same for diabetic nephropathy.[19] The management follows a multi-disciplinary approach, with blood glucose control, pharmacologic intervention, lifestyle modification, and changes.[19,20] Other treatment strategies include hemodialysis, peritoneal dialysis, and transplantation.

STRICT GLYCEMIC CONTROL

Studies have shown that patients able to control their blood glucose for a long time and maintain it have a reduced risk of progressing to nephropathy.[20] It also contributes to reducing the risk of deterioration of diabetic nephropathy and the development of microalbuminuria and macroalbuminuria, as shown in the Action in Diabetes and Vascular Disease: Preterax

and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.[20,21]

SGLT2 inhibitors improve kidney hypoxia, correct glomerular hyperfiltration, promote urinary glucose excretion, and inhibit proximal tubular glucose reabsorption. Empagliflozin in Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was shown to reduce cardiovascular events and progression of nephropathy in patients with type 2 diabetes. Canagliflozin in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) was similarly efficacious in DKD patients with type 2 diabetes.[19] Canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program reduced the estimated glomerular filtration rate by 40%, inhibiting the progression of albuminuria and delaying overall the progression of DKD.[20] SGLT2 inhibitors are also more efficacious when used with RAS inhibitors.[19]

ACEIs/ARBs

Current treatments for DKD include Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II receptor blockers (ARB), which inhibit the Renin-Angiotensin system (RAS), mineralocorticoid receptor antagonist, Sodium-glucose cotransporter 2 (SGLT2) inhibitors.[19]

RAS inhibitors are effective in all stages of DKD and prevent the progression of DKD, which occurs due to glomerular hypertension, production of reactive oxygen species, accumulation of extra-cellular matrix, and inflammatory cytokines because of overactivation of the RAS.[19]

Ramipril has been found to retard progression in 1 diabetic patients with overt nephropathy and to impede renal function loss.[19,22] ARBs such as Losartan and Irbesartan have also been shown to reduce microalbuminuria, with the latter inhibiting by 70% the progression of microalbuminuria to overt nephropathy in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2).[19,23] Telmisartan compared to placebo in The Incident to Overt: Angiotensin II receptor blocker, Telmisartan, Investigation On type II diabetic Nephropathy (INNOVATION) study in Japan was shown to prevent microalbuminuria from progressing to overt nephropathy by 60%. Compared to a calcium channel blocker, the use of ARB only in the Microalbuminuria reduction with valsartan (MARVAL) showed that they were very effective in lowering and preventing microalbuminuria.[19]

By blocking the action of aldosterone, mineralocorticoid receptor antagonist (MRA) drugs have antihypertensive effects and reduce proteinuria.[19,24] Spironolactone reduced the incidence of renal fibrosis, inflammation, and albuminuria in DKD patients. Eplerenone, another member of the drug class, was found to reduce albuminuria in patients with systemic hypertension. The adverse side effects of these drugs, such as hyperkalemia in patients with CKD, led to the development of newer non-steroidal MRA drugs, such as Finerenone and Esaxerenone, which are more selective for the mineralocorticoid receptor, with a better adverse risk profile compared to the older drugs and equally as effective in reducing proteinuria in DKD patients.[19]

NEWER MOLECULES

1. Newer treatment options for DKD include NF-E2-related factor 2 (Nrf2) activator, Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor, Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DDP4) inhibitors which are incretin-based drugs, Advanced Glycosylation End products (AGE) inhibitors.[19] Others include Pentoxifylline, Vitamin D, Avosentan, Ruboxistaurin, and Sulodexide.[20]

2. Suppressing HIF-PH inhibitors prevents the degradation of the Hypoxia-inducible factor (HIF), a transcription factor in response to hypoxia. HIF activation has been shown to suppress tubular cell apoptosis and promote cell proliferation and regeneration, with renoprotective effects. In a type 2 diabetes mouse model, a HIF-PH inhibitor significantly reduced albuminuria and glomerular inflammation.[19]

3. GLP-1 receptor agonists and DDP4 inhibitors have renoprotective and hypoglycemic effects. The Incretin-based drugs have been shown in several studies to decrease albuminuria in DKD patients.[19] In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), the patients in the GLP-1 receptor agonist group were found to have decreased overt albuminuria. In addition, in dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7) trial, a decrease in the rate of eGFR reduction and reduced albuminuria was observed in those in the Dulaglutide group.[19]

4. AGE accumulation has been linked with the progression of DKD.[1] Pyridoxamine in the pyridoxamine (PYR)-206 and PYR 205/207 studies was after six months of treatment in DKD patients found to reduce urinary TGF-β1 excretion and also a change from baseline in

serum creatinine.[19] Patients with normal renal function in the Pyridoxamine phase II trial also had lower serum creatinine levels.[20]

5. Pentoxifylline has been shown to reduce the rate of renal fibrosis and decrease urinary albumin excretion when used with RAS inhibitors.
6. Vitamin D analogs with ARB prevented kidney injury, and the Selective Vitamin D Receptor Activator for Albuminuria Lowering (VITAL) study reduced albuminuria by 18% -28 %.
7. Sulodexide, a glycosaminoglycan mixture, has also been found to reduce urinary protein excretion significantly.[20]

PREVENTION

Strict glycemic control is the foundation of the prevention of DKD. The prevention of its risk factors also plays an important role in the primary prevention of the disease. Strict glycemic control has been found to significantly lower the risk of microalbuminuria and structural and clinical manifestations of DKD.[25,26] In type 2 DM patients, dietary modification such as reduced fatty food, consumption of legumes and nuts, intake of 0.7-0.9g of protein/kg body weight/day, and phosphorus of 500mg to 1g/day has been found to retard the progression of nephropathy.[26]

Lifestyle modifications such as weight reduction, smoking cessation, exercise, and increased physical activity are also essential in preventing DKD. Dietary restriction of potassium and particularly sodium is beneficial in DM patients with proteinuria.[20] These are particularly important in developing countries, as managing patients with DKD with medications can be prohibitively expensive.[27] They have also been shown, in the Steno-2 trial, to reduce the occurrence of cardiovascular events and impede the progression of DKD.[19]

Regular screening for proteinuria, especially with the dipstick urinalysis, which can be easily performed as an office procedure or at health outreaches, ensures that cases are picked up at early stages, progression is retarded, and complications are prevented.[28] This applies especially to developing countries where health-seeking behavior is generally poor, and patients only present at healthcare facilities once complications arise and the prognosis is poor.

Adherence to drug treatment, lifestyle modifications, and other measures to prevent disease progression should be emphasized and encouraged, and patients should be referred to support groups and networks if available. Furthermore, as patients with microalbuminuria usually have concomitant hypertension and dyslipidemia contributing to adverse cardiovascular events, low-dose aspirin is recommended to prevent cardiovascular events.[26] This is an effective measure that would contribute to the overall outcome of patients with DKD.

In developing countries where the general population has to pay out of pocket for health services, the government can implement policies such as including treatment for DKD in the health insurance schemes, subsidizing the cost of medications and insulin, improving public awareness and health education about signs and symptoms of the disease which would in turn lead to early presentation of cases at hospitals. As further research is ongoing concerning the disease, the government can also encourage researchers by providing grants and improving infrastructure to carry out research.

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