Title

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Journal

Journal of the National Medical Association, 114(3)

ISSN

0027-9684

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Publication Date

2022-06-01

DOI

10.1016/j.jnma.2022.05.004

Peer reviewed

Published in final edited form as:

J Natl Med Assoc. 2022 June ; 114(3 Suppl 2): S3–S9. doi:10.1016/j.jnma.2022.05.004.

Etiopathogenesis of Kidney Disease in Minority Populations and an Updated Special Focus on Treatment in Diabetes and Hypertension

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Abstract

Diabetes and hypertension are the most common causes of chronic kidney disease (CKD) in the general population as well as in the Black and African American population, who also suffer from high rates of CKD and CKD progression compared to the White population. Progression of CKD can lead to kidney failure, and patients with progressive kidney disease have a high risk of premature mortality, particularly from cardiovascular disease. Screening for early detection of CKD is important as it facilitates the initiation of medications that have shown to delay the progression of diabetes-related as well as non-diabetes-related CKD, and reduce rates of death from both kidney and cardiovascular disease. The potential adverse effects from use of some of the newer reno- and cardio-protective glucose-lowering medications, such as the sodium glucose cotransporter-2 inhibitors may be effectively avoided with detailed patient education and monitoring by the healthcare provider. It is important to note that lifestyle modification including regular exercise, diet and smoking cessation are first-line in the management of diabetes and hypertension. When CKD occurs, co-management by providers using a comprehensive strategy may avert early complications and facilitate appropriate early referral for nephrology specialty care.

Keywords

diabetes; hypertension; chronic kidney disease; angiotensin converting enzyme inhibitors; angiotensin receptor blockers; sodium glucose co-transporter-2 inhibitors

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ETHICS APPROVAL
This is a review article, therefore institutional approval and patient consent were not required.

CONSENT FOR PUBLISHING
All authors gave their consent for publishing.

INTRODUCTION

Diabetes is a global pandemic, and both diabetes and hypertension are the most common causes of kidney failure. Unfortunately, Black and African Americans suffer disproportionately from diabetes, hypertension (HTN) and their related chronic kidney disease (CKD). Due to the silent nature of these disorders in which symptoms do not appear until late in the course of the diseases, screening and early diagnosis for individuals who may be at risk for CKD from diabetes and HTN, for instance due to a medical history of obesity, smoking, use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, acute kidney injury, or a family history of diabetes, HTN, and/or kidney disease is crucial. As soon as patients are identified with CKD due to diabetes or HTN, a comprehensive, multidisciplinary approach with the initiation of lifestyle modification as first-line therapy is warranted, followed by appropriate institution of medications proven to have both renal and cardiac protection. As CKD begins to progress, early referral to nephrology specialty care may avoid further complications and facilitate timely preparation for renal replacement therapy. This review provides a brief and succinct description of the salient features to promote judicious management of HTN, and diabetes and CKD with considerations for the general population, and for racial and ethnic minority populations. Since the introduction twenty years ago of renin-angiotensin-aldosterone system (RAAS) antagonists, specifically angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor antagonists (ARBs), new classes of cardio-protective agents that also have reno-protective properties have become a part of the arsenal to treat diabetes and non-diabetes-related CKD. Given the elevated cardiovascular-related mortality rates associated with CKD, it is the hope that this review will provide sufficient information/education to increase the usage rates of cardio- and reno-protective agents in this patient population.

Epidemiology of hypertension in the general population

Hypertension is the most common chronic medical condition in the United States (US),[1] the second most preventable cause of death only after smoking,[2] a risk factor for adverse cardiovascular outcomes and premature morbidity and mortality, and a key public health concern.[1] It is also the second leading cause of CKD and kidney failure or end stage kidney disease (ESKD) in the US.[3] Nearly half of US adults (47% or 116 million) have a history of HTN[4] and 67–92% patients with CKD have HTN.[2]

Epidemiology of hypertension in the Black or African American population

Hypertension is more common in African Americans (56%), compared to White Americans (48%), Asian Americans (46%) and Hispanic Americans (39%).[5] In particular, masked HTN (defined as normal office blood pressure (BP) but elevated out-of-office BP)[6] and nocturnal HTN (night-time BP >110/65 mm Hg)[2] are more common in African Americans and confer increased adverse cardiovascular and kidney disease risk.[7]

Pathogenesis of hypertension in the general population

Blood pressure control is determined by the cardiac output, blood volume, arterial tone, and neurohormonal cascades (including the RAAS) which interplay to regulate BP.[8] Failure of any of these components to compensate for changes can lead to BP variability and end organ

damage.[8] Genetic predisposition and environmental factors such as stressors or poor diet increase the likelihood of HTN.[8] In addition, the development of atherosclerosis and arterial stiffening due to vascular collagen changes with aging increase the likelihood of HTN.[8]

Pathogenesis of hypertension in African Americans

Salt avidity which increases BP by causing fluid retention and blood volume expansion in the presence of endothelial dysfunction may account for greater increases in BP in African Americans with similar salt loads as seen in other racial and ethnic groups.[8] Other possible causes of the increased prevalence of HTN in African American communities include chronic social stressors, poor diet, inadequate pre-natal care, low access to medical care, high prevalence of obesity, and the development of HTN in youth.[9] In addition, lower potassium intake in African Americans compared to Whites[10] may increase sodium retention causing increased BP,[11] although this association is less clear in patients with diagnosed HTN as opposed to non-hypertensive patients.[11] An important aspect of HTN in African Americans is the increased related risk of progression to kidney failure due to HTN.[12] Further, apolipoprotein L1 gene high-risk alleles are known to be associated with a greater risk for incident HTN, greater odds of incident albuminuria, and an increased risk for kidney disease and kidney failure in African Americans.[13]

Updated targets for blood pressure control

In contrast to the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) HTN guidelines which recommend a BP goal of <130/80 mm Hg for patients with CKD and concerns for adverse effects of a lower BP target,[1, 2] the 2021 Kidney Disease Improving Global Outcomes (KDIGO) Hypertension Guideline considered more recent data to update BP goals in patients with CKD.[4] In keeping with the Randomized Trial of Intensive versus Standard Blood-Pressure Control (SPRINT) trial findings, the KDIGO Guideline recommends systolic BP targets of <120 mm Hg, when tolerated in patients with HTN and CKD based on the SPRINT-study-demonstrated association of lower systolic BP with reduced cardiovascular and all-cause mortality.[4, 14] Regardless of the target BP, both the 2021 KDIGO and the 2017 ACC/AHA HTN guidelines recommend adoption of lifestyle modifications including moderate intensity exercise for ≥150 minutes per week, and a low sodium (<2 g/day) diet in the management of HTN in patients with CKD.[1, 4] Notably, a lower sodium diet (<2g/day) may result in greater reduction in BP in African American populations compared to White Americans.[1] The KDIGO Guideline also suggests that other lifestyle interventions such as weight loss, cessation of alcohol consumption, and heart healthy dietary patterns (such as the Dietary Approaches To Stop Hypertension (DASH) diet) may be beneficial in patients with CKD,[4] however there is currently insufficient evidence of risks and benefits in CKD patients with HTN, and thus no specific recommendations in the area have been provided.[2, 15] Although, patients with CKD were excluded from the original DASH study, subsequent studies have shown that adherence to a diet rich in fruits, vegetables, lean meats, and whole grains is associated with lower BP in African American patients with CKD,[16] and decreased risk of CKD development.[17, 18] However, in advanced CKD, the KDIGO Guideline cautions against a potassium-rich diet which exceeds the recommended potassium intake of 120 mmol/day.[4, 11]

Further study is needed to determine whether adherence to the DASH diet prevents or delays CKD progression, especially in African American patients.[18, 19]

Treatment of hypertension

Maximal RAS inhibition with ACEIs or ARBs is recommended in patients with HTN, CKD, and moderate to severe albuminuria with or without diabetes.[4] ACEIs/ARBs, or other direct renin inhibitors should not be used in combination given the increased risk of adverse effects such as hyperkalemia and acute kidney injury, as well as the lack of significant increase in cardiovascular or kidney related benefits despite declines in proteinuria.[2, 4]

Treatment of hypertension specific to African Americans

In African American patients with HTN, but without heart failure or CKD, it has been recommended that thiazide-type diuretics or calcium channel blockers are used initially for BP control given their more effective antihypertensive effects and decreased cardiovascular disease-related events compared to other drug classes.[2, 10] However, therapy with any combination of thiazide diuretics, dihydropyridine calcium channel blockers, ACEIs/ARBs is reasonable to decrease cardiovascular or renal outcomes in patients with HTN.[2] In light of the higher risk of treatment-resistant HTN in African American compared to White patients,[2, 10] more than three agents may be necessary to achieve BPs within the target range for African Americans.[2] This observation should prompt confirmation of medication adherence as well as trigger evaluation for alternative or secondary causes of HTN in these patients. Of note, younger (<60 years of age) African American patients are ~40% less likely to achieve hypertensive control than their White counterparts.[10] A host of patient and healthcare system related factors affect HTN control in African Americans including low rate of disease awareness, inadequate lifestyle modification, in addition to social and cultural patterns affecting disease, medication adherence, access to adequate healthcare, appropriate clinical follow-up, and shifting standards and targets in HTN management.[10] A higher potassium diet has been suggested due to the concern that a low potassium diet may contribute to salt sensitivity in African Americans, but this is an area of ongoing study.[11] Despite notable advances in CKD management over the last 20 years, optimal management of HTN remains a critical target in delaying CKD progression and preventing increased morbidity and mortality in Black or African Americans especially given the disproportionate disease burden in this population.[2, 3]

Epidemiology of diabetes in the general population

Diabetes is a global pandemic.[20] In 2010, the prevalence was expected to increase from 300 million to 438 million in 2025, but had already reached 463 million by 2020, driven in part by combined effects of population aging, and rising levels of obesity and inactivity.[20] A total of 34.2 million people (10.5% of the US population) and 88 million people (34.5% of the US adult population) have diabetes and pre-diabetes respectively.[5]

Epidemiology of diabetes and CKD in Black and African Americans

The Black and African American populations, compared to the White population experiences higher rates of diabetes and its complications, with a 1.6-and 2-fold higher risk

of developing diabetes as well as death from diabetes, respectively,[3] and a 2.5 fold higher risk of developing ESKD from diabetes.[21] Further, Black and African American patients experience worse clinical outcomes associated with diabetes including a 1.3-fold, 2.3-fold, and 3-fold higher risk of visual impairment secondary to diabetes, hospitalizations for lower limb amputations, and uncontrolled diabetes without complications respectively,[3] and a 1.3-fold higher risk of death from heart disease, compared to their White peers.[12] Ethnic disparities in diabetic complications and increased susceptibility to diabetic nephropathy and ESKD are not fully explained by demographics, socioeconomic disparities, modifiable behavioral outcomes, or clinical characteristics, suggesting that genetic risk may play a role. Black and African American patients have a longer survival after kidney failure onset and account for 35% of the ESKD patients in the US.[22]

Pathogenesis of kidney disease in patients with diabetes

Kidney disease in patients with diabetes may be defined clinically as diabetic kidney disease (DKD) marked by estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, or UACR >30 mg/g, or both, with clinical signs of diabetes.[23, 24] On the other hand, diabetic nephropathy refers to structural features from a kidney biopsy showing hallmark pathologic lesions consisting of increased glomerular basement membrane thickening, mesangial expansion, nodular lesions, damage to podocytes including podocyte effacement and/or podocyte loss, and endothelial disruption.[24] The pathophysiologic mechanisms of diabetic nephropathy involve renal hemodynamic changes, overactive RAAS, hypoxia, oxidative stress and inflammation all of which may contribute to renal fibrosis.[25, 26] Importantly, the clinical syndrome of DKD is associated with increased cardiovascular events and mortality.[25]

Factors related to racial and ethnic minority populations

Observed disparities in the prevalence of diabetes and CKD are attributed to the complex interplay of social, cultural and environmental, as well as genetic and biological factors in racial and ethnic minority populations.[27] Geographically tagged disease-associated single nucleotide polymorphisms from the Human Genome Diversity panel reveal genetic variation in type 2 diabetes risk with the highest risk observed in Black and African American populations, lowest risk in Asian populations, and intermediate risk in Middle Eastern populations.[13] In addition to biologic mechanisms underlying DKD, markers such as high sensitivity-C-reactive protein have been linked with incident DKD in Black and African Americans.[27]

Standard of care approaches to management of patients with DKD

The American Diabetes Association recommends early diagnosis of CKD in patients with diabetes with at least annual screening for urine albumin-to-creatinine ratio and eGFR.[28] Appropriate referral to nephrology specialty care are key features in management, and efforts such as provider-delivered culturally sensitive education and authentic stakeholder engagement are critical to leverage trust, and optimize the uptake of annual and community screening for kidney disease.[28, 29] Management of CKD in diabetes involves a comprehensive strategy including therapy targeting glycemic, BP and lipid management; and lifestyle changes including exercise (moderate-intensity physical activity for ≥150

minutes per week if compatible with physical and cardiovascular tolerance) nutrition (protein intake of 0.8 protein/kg for non-dialysis patients) and smoking cessation, to reduce risks of kidney disease progression and cardiovascular disease.[23] In addition to lifestyle approaches, glycemic management for patients with diabetes and CKD should include therapy with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT-2 inhibitor), and additional drug therapy as needed for glycemic control, TABLE 1. Selection of glucose-lowering drugs other than an SGLT-2 inhibitor and metformin in type 2 diabetes and DKD should be based on patient-centered factors. A long-acting glucagon-like peptide-1 receptor agonist (GLP1 RA) is recommended for patients with type 2 diabetes and CKD who have not achieved glycemic control despite use of metformin and an SGLT-2 inhibitor, or who are unable to use those medications.[23]

First-line pharmacologic renoprotective therapy with RAAS blockade using an ACEI or ARB should be instituted in patients with diabetes, HTN and albuminuria and titrated to the highest tolerated approved dose.[23] An SGLT-2 inhibitor may be added for both cardiovascular (empagliflozin, canagliflozin, dapagliflozin), and renal protection (canagliflozin, dapagliflozin), which may provide an additional 15 years of kidney health.[30–32] In essence, while SGLT-2 inhibitors were first introduced as glucose-lowering drugs, in fact their metabolic benefits are relatively low, especially in advanced CKD,[33] and they have evolved as primarily kidney and cardiac protection medications. Importantly, SGLT-2 inhibitors may be initiated following ACEI/ARB when the eGFR is >30 ml/min/1.73 m^2, and maintained until the eGFR falls to 25 ml/min/1.73 m^2, but discontinued once the patient starts chronic renal replacement therapy including kidney transplantation.[23]

Sodium glucose transporter-2 inhibitors may be associated with a number of potential adverse effects, all of which may be appropriately averted with detailed patient education and provider surveillance.[34] For example, it is recommended that once an SGLT-2 inhibitor is initiated, patients should be advised to maintain adequate hydration daily to avoid dehydration and/or hypotension due the polyuria effect of the drugs, which may increase with the severity of glycemia. Also, diuretic dosing may need to be adjusted. To avoid genital infections, basic genital hygiene should be encouraged and patients should seek immediate medical attention for symptoms of urogenital infection or urinary tract infections. In some instances, the SGLT-2 inhibitor may need to be discontinued in patients with recurrent urinary tract infections, or held temporarily when fasting, during an acute illness (i.e. having a ‘sick-day’) or perioperatively. Although the absolute risk of euglycemic diabetic ketoacidosis with SGLT-2 inhibitors is relatively low, patients should be monitored with blood ketone measurements (as urine ketones are unreliable) if they feel unwell or have symptoms of nausea or vomiting when fasting. Other conditions that may predispose to euglycemic diabetic ketoacidosis include excess alcohol intake and female gender.[35] Although, meta-analyses have shown no increases in SGLT-2 inhibitor-related amputations,[36] patients should have regular podiatry care and the drug may need to be avoided when there is evidence of compromised peripheral vascular supply.

In addition to SGLT-2 inhibitors, the non-steroidal mineralocorticoid receptor antagonist, finerenone was the first of its class to receive approval for cardio-protection and to fill the residual renal risk left by ACEI/ARB and SGLT-2 inhibitors by targeting anti-fibrotic

and anti-inflammatory processes.[37, 38] Although mild-moderate hyperkalemia may occur with use of finerenone compared to placebo, the rates of clinical consequences are low and patients may do well with dietary restriction, where indicated. It should be noted that a host of novel DKD agents targeting anti-fibrotic and anti-inflammatory pathways for reno-protection are currently in clinical trials.[26]

Medication adherence is an important modifiable self-care practice in diabetes and CKD[39] that reduces existing racial disparities. Thus it should be prioritized as an intervention target especially among Black and African American patients who report sub-optimal mediation adherence compared to White patients[40] and experience several barriers to optimal management of diabetes that are driven by structural racism.[41] In an effort to improve optimal care for Black and African American patients, health care systems should consider implementing structured self-management programs for patients with diabetes and CKD, prioritizing local context, cultures and availability of resources.[23]

CONCLUSIONS AND IMPLICATIONS

Hypertension, diabetes and CKD disproportionately affect the Black and African American population, and can lead to kidney failure and premature death if not caught early and managed appropriately. Implementation of specific guidelines set by the ADA, ACC/AHA and KDIGO are important to prevent the potential sequelae from these diseases. Indeed, guidelines recommend initial lifestyle modification, and the subsequent or concurrent use of RAAS blockers and newer agents that have been shown to delay CKD progression as well as prevent death from kidney and cardiovascular disease. Providers should be aware of the risk factors that contribute to the development and progression of CKD and engage in CKD co-management with other specialty care providers. It is important to educate patients on disease-related signs and symptoms and potential adverse effects of pharmacologic therapy and to encourage medication adherence.

Sources of support:

This work was supported in part by NIH NIDDK 1K23DK114566-01A1 and NIH NIDDK 1 R03 DK129626-01 (Umeukeje), and NIH NIMHD R01MD014712-01 (Nicholas)

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Table 1.

Standard of care approaches to the management of patients with diabetes and chronic kidney disease

EARLY INTERVENTION
Annual screening for urine albumin-to-creatinine and eGFR
Early referral to nephrology
Provider-delivered culturally sensitive education
Authentic stakeholder engagement
LIFESTYLE CHANGES
Exercise: moderate-intensity physical activity for ≥150 minutes/week
Smoking cessation
Nutrition: protein intake of 0.8 protein/kg for non-dialysis patients
COMPREHENSIVE CARE APPROACH
Blood pressure management
Lipid management
Glycemic management
Glycemic management
First line therapy: Metformin plus SGLT-2 inhibitor
Selection of non-first line therapy: should be based on patient-centered factors
Additional therapy as needed to optimize glycemic control e.g. GLP1 RA
Kidney protective therapy
First line renoprotective therapy: RAAS blockade with ACEI or ARB
Second line therapy: SGLT-2 inhibitor
• Renal protection: *canagliflozin, dapagliflozin*
• Cardiovascular protection: *canagliflozin, dapagliflozin, empagliflozin*
• Initiate at eGFR ≥30 ml/min/1.73 m^2; maintained until >25 ml/min/1.73 m^2
• Discontinue once renal replacement therapy is initiated
Key take home points related to use of SGLT-2 inhibitor
Initiate at eGFR ≥ 30 ml/min/1.73 m^2; maintain until >25 ml/min/1.73 m^2
Discontinue once renal replacement therapy is initiated
Avoid dehydration/hypotension due to polyuria
Adjust diuretic dosing if need be
Observe basic genital hygiene to avoid genital infections
Check blood ketones to rule out euglycemic diabetic ketoacidosis if patients have nausea, vomiting
Regular podiatry care and avoid use if evidence of compromised peripheral vascular supply

eGFR: estimated glomerular filtration rate, SGLT-2: sodium-glucose cotransporter-2, GLP1 RA: glucagon-like peptide-1 receptor agonist, RAAS: renin angiotensin aldosterone system, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker