DIABETES MELLITUS AND HYPERTENSION: KEY RISK FACTORS FOR KIDNEY DISEASE

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The incidence of end-stage renal disease (ESRD) in the US is rising at an alarming rate, with the largest increase among African-American populations. The key risk factors for kidney disease are hypertension and diabetes, which are both becoming more prevalent in the US, and particularly in African Americans. Although African Americans make up 12.6% of the US population, the incidence of diabetes-related ESRD is four times higher than for whites, and the prevalence of ESRD due to hypertension is twice that of white patients. Approximately 30 to 40% of all patients with diabetes will develop nephropathy and many will progress to ESRD, necessitating dialysis or kidney transplantation. Recent studies in patients with type 2 diabetes indicate a significant delay in progression or development of diabetic nephropathy following blockade of the renin–angiotensin–aldosterone system with the use of angiotensin receptor antagonists.

Early intervention in patients with hypertension is necessary to prevent kidney damage, and data from the African American Study of Kidney Disease and Hypertension suggest that angiotensin-converting enzyme inhibitors are effective in this population. Although African-American patients receiving hemodialysis appear to have increased survival compared with whites, racial factors and poor access to medical care contribute to the increased risk of kidney disease in minorities. A concerted effort is necessary to raise awareness in minority populations and provide strategies for prevention and early treatment thereby attenuating the increasing prevalence of kidney failure in these groups.

Key words: end-stage renal disease ♦ diabetes ♦ hypertension ♦ kidney disease

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) affect an increasing proportion of the population in the US.[1–3] The Third National Health and Nutrition Examination Survey (NHANES III) recently estimated the prevalence of CKD (defined as a serum creatinine level of ≥ 1.5 mg/dL) in the US to be approximately 6.2 million,[4] and the number of patients with ESRD is expected to almost double in the next 10 years.[5] In general, the most common causes of ESRD are diabetes and hypertension (Fig. 1).[5]

A major risk factor for the development of type 2 diabetes is obesity.[6] Therefore, it is thought that the dramatic increase in the incidence of ESRD that has been observed over the past 20 years is attributable to the epidemic of type 2 diabetes that has occurred during this time. At present, approximately 15.6 million Americans have diabetes, predominantly type 2 diabetes. A further 13.4 million have impaired glucose tolerance,[7] and 50 million have hypertension.[8] However, the prevalence of diabetes, hypertension, and obesity is significantly higher in African Americans than in whites, particularly in the Southeastern region of the US. In fact, the prevalence of hypertension in African Americans is among the highest in the world.[9]

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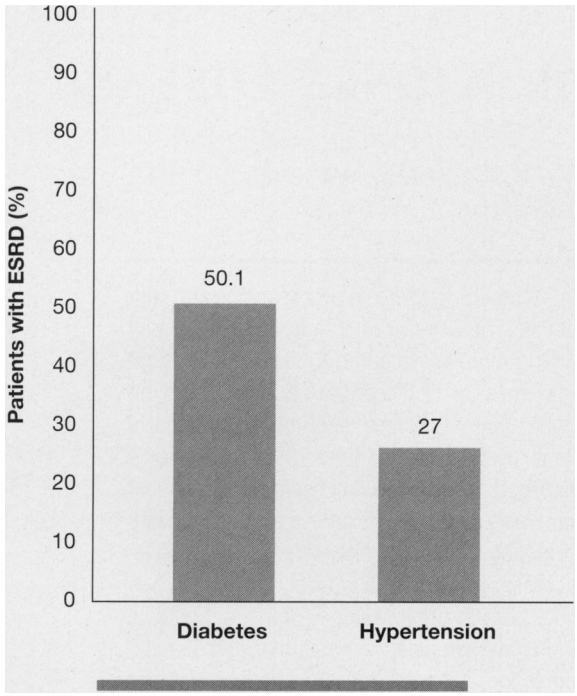

Figure 1. Primary Causes of ESRD.[5]
Data from US Renal Data System 2000.

As a result, the adjusted incidence of ESRD among African Americans in the Southeastern US has been estimated to be up to 15-fold greater than in whites.[10] In addition, even when hypertension is well-controlled, there is a tendency for African Americans to suffer impairments in kidney function.[11,12]

Recently, the African-American Study of Kidney Disease and Hypertension (AASK) examined the role of the renin–angiotensin–aldosterone system (RAAS) and the use of angiotensin-converting enzyme (ACE) inhibitors in the management of hypertension, specifically in African Americans.[13] Preliminary findings have demonstrated that ACE inhibitor therapy can effectively improve blood pressure (BP) and significantly reduce the rate of rise of serum creatinine levels and time to ESRD.[14] In addition, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Type II Diabetic Nephropathy Trial (IDNT) studies have reported the effect of angiotensin receptor antagonism on delaying the progression and development of diabetic nephropathy in hypertensive type 2 diabetics. These studies were performed in large populations with representative (~14%) African-American enrollment.[15,16] These studies have demonstrated that blockade of the RAAS via angiotensin receptor blockade can also improve BP, and attenuate a rise in serum creatinine levels and the time to ESRD. However, the lessons learned from these latter studies can only be useful if patients are monitored aggressively, not only for BP and blood glucose, but also for early detection of proteinuria and deterioration in kidney function.

This review will focus on the two main causes of the increase in the prevalence of ESRD, diabetes and hypertension. It will also discuss reasons for disparities between populations, highlight risk factors in the post-transplant period, explore factors contributing to suboptimal care in these patients, and propose steps to address these issues.

REASONS FOR RACIAL DISPARITIES IN KIDNEY DISEASE

Demographic data suggest that those most susceptible to ESRD are the elderly (> 65 years of age), those of low socioeconomic status, and minority groups, particularly African Americans.[10] In addition, data from the Multiple Risk Factor Intervention Trial (MRFIT) and Modification of Diet in Renal Disease (MDRD) study suggest a significantly greater rate of loss of kidney function in African Americans with hypertension compared with whites.[12,17,18] Taken together, these data suggest that African Americans possess a unique susceptibility to kidney disease.

A complex interplay of genetic, cultural, social and environmental influences, as well as healthcare inequities, play a part in the racial disparities associated with kidney disease.[19–21]

Diets high in calories, carbohydrates, and sodium, but low in potassium, magnesium, and

calcium, are common in minority populations, and may contribute to the higher prevalence and severity of hypertension among African Americans compared with whites.[22] African-American patients with hypertension have higher rates of salt sensitivity, and recent evidence suggests that this causes higher rates of left ventricular hypertrophy, higher serum creatinine levels, and increased urinary albumin excretion, as well as retinopathy.[23] High sodium diets increase BP,[24] and so raise intraglomerular pressure in salt-sensitive patients, which may contribute to the propensity for kidney failure in African Americans. How sodium sensitivity increases the risk of cardiovascular events remains unknown, but it may be due to concurrent microalbuminuria. Clustering of several factors with well-known atherogenic potential, including hyperinsulinemia, hyperlipidemia, and microalbuminuria, in salt-sensitive hypertensive patients may explain, in part, their increased risk of cardiovascular disease. In fact, this metabolic syndrome, also termed syndrome X, is associated with obesity and type 2 diabetes, and may be more prevalent in African Americans.[25]

In fact, the increasing racial disparities in diabetic nephropathy in African Americans may be directly related to the increased incidence of obesity, particularly in African-American females who demonstrate the highest prevalence, as well as high rates of low levels of exercise and poor dietary habits. The increased incidence of obesity in minority children also extends into adulthood and may have a direct impact on the increased risk for cardiovascular disease.

DIABETES MELLITUS AS A CAUSE OF KIDNEY DISEASE

Diabetes mellitus is a metabolic disorder characterized by absolute (type 1) or relative (type 2) insulin insufficiency. Patients with diabetes can develop kidney disease and about one-third develop diabetic nephropathy, which accounts for almost half of new ESRD cases.[5]

Pathogenesis of Diabetic Kidney Disease

Early in the course of diabetic nephropathy, changes in kidney hemodynamics and hyperfiltration lead to an increase in glomerular filtration rate (GFR).[26] The progression of nephropathy involves characteristic pathologic changes, including accumulation of the extracellular matrix, widening of the glomerular basement membrane, arteriosclerosis, and some degree of interstitial fibrosis.[27] To date, there is no evidence of any significant difference in the histologic changes that occur in African Americans and whites.

The earliest clinical manifestation of diabetic nephropathy is microalbuminuria (20 to 200 μg/min), which, if left untreated, can progress to overt nephropathy after 10 to 15 years of diabetes, and is also a marker for cardiovascular disease.[27] In African Americans, albuminuria may be present in 30 to 40% of patients with diabetic nephropathy.[28,29] However, delayed diagnosis and poorer control of plasma glucose and BP among African-American patients reduce the chances of improvement and resolution of microalbuminuria. Some of the clinical features that are characteristic of type 2 diabetic nephropathy are listed in Table 1.

Although, poor glycemic control and hypertension are the major risk factors in African Americans that contribute to a more rapid progression to ESRD, other putative risk factors

Table 1. Clinical Features of Type 2 Diabetic Nephropathy

- Most common after 40 years of age
- Abdominal obesity present in 90% of patients
- Insulin resistance/hyperinsulinemia
- Ketosis resistance
- Hypertension common
- High very low density lipoprotein, low high density lipoprotein cholesterol
- Accelerated atherosclerosis
- Increased prevalence in African Americans, Mexican Americans, and Native American Indians

include obesity, genetic factors, low birth weight, endogenous hyperinsulinemia, elevated triglyceride levels and decreased access to healthcare.[30,31] However, it is uncertain whether these factors precede, or are simply associated with, the pathologic process. At the molecular level, numerous cytokines, growth factors and hormones such as transforming growth factor-beta (TGF-β), and angiotensin II play an important role in promoting the pathologic and histologic changes that are characteristic of diabetic nephropathy.[32,33]

Optimal glycemic control with sulfonylureas, insulin, and newer therapies, such as thiazolidinediones, are important in diabetes management and the progression of diabetic nephropathy. When these medications are combined with regular screening and lifestyle modification, such as anti-hypertensive therapy, smoking cessation, lipid control and ongoing, intensive patient counseling, a significant reduction in morbidity and delay in progression of diabetic nephropathy can be achieved.[34,35]

Lessons Learned from RENAAL and IDNT

It has been known for some time that the RAAS plays an important role in the pathologic process of diabetic nephropathy and that the use of ACE inhibitors is effective in delaying progression of disease in patients with type 1 diabetes as well as in non-diabetic patients with overt nephropathy.[36] However, data supporting the use of angiotensin blockade for type 2 diabetes has only recently become available. The RENAAL and IDNT trials specifically used angiotensin II receptor antagonists (losartan or irbesartan) alone or combined with conventional anti-hypertensive therapy, in hypertensive type 2 diabetic patients with nephropathy and a body mass index (BMI) > 29 kg/m^2. The RENAAL trial investigated whether this approach would increase the time to doubling of the serum creatinine concentration, the onset of ESRD, or death. Secondary endpoints determined the effect of losartan or placebo on morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of kidney disease. The IDNT study also assessed the composite time to doubling of the serum creatinine concentration, ESRD, or death with secondary endpoints, which included cardiovascular death. African Americans comprised 14 to 15% of the study population in both trials. The use of losartan resulted in a delay in the progression to ESRD and decline of kidney function, and decreased proteinuria. In addition, the use of irbesartan delayed the need for kidney transplantation or dialysis. Of note, these positive results were independent of a BP effect.[37] A further trial also showed that irbesartan can be renoprotective in hypertensive, type 2 diabetic patients with microalbuminuria; however, significantly fewer African Americans were enrolled in this study.[38]

HYPERTENSION AND KIDNEY DISEASE

Hypertension is a well-characterized risk factor for ESRD, and accounts for 27% of all ESRD cases in the US[5] and 33.4% of ESRD cases among African Americans.[39] There is a progressive increase in the risk of ESRD with increasing BP as shown by analysis of the MRFIT study, which classified BP according to the five criteria of the Joint National Committee (JNC 5) on prevention, detection, evaluation, and treatment of high BP (Table 2).[40] Analysis of the data collected from 332,544 men over a 16-year period in the MRFIT study showed that the adjusted relative risk of developing ESRD was 1.9 for high–normal BP, 3.1 for stage 1, 6.0 for stage 2, 11.2 for stage 3, and 22.1 for stage 4 hypertension, relative to the category of optimal BP (systolic BP < 120 and diastolic BP < 80 mmHg) (Fig. 2).[40] A recent analysis by Coresh and colleagues evaluated over 17,000 adults in the NHANES III database, a cross-sectional, nationally representative sample of the US civilian non-institutionalized population. They reported that elevations in serum creatinine levels were strongly related to inadequate treatment of high BP, consistent with results from the MRFIT study.[41] Not only is hypertension a major cause of kidney failure, but evidence also indicates that

Table 2. JNC 5 Classification of Blood Pressure for Adults 18 Years of Age and Older[40]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	< 130	and	< 85
High–normal	130–139	or	85–89
Hypertension			
Stage 1	140–159	or	90–99
Stage 2	160–179	or	100–109
Stage 3	180–209	or	110–119
Stage 4	≥ 210	or	≥ 120

Data from Klag et al. 1996.

coexistent hypertension plays a predominant role in the relentless downhill progression of most CKDs, including diabetic nephropathy.[17,42]

Pathogenesis of Hypertension and Kidney Disease

Essential hypertension is typically recognized in subjects between 25 to 45 years of age but kidney impairment remains uncommon until the patient has experienced at least 10 years of sustained hypertension. In these patients, increased BP results in the development of arteriolar nephrosclerosis with impaired kidney function (Table 3). If hypertension is superimposed on intrinsic kidney disease, this adds to the progressive loss of kidney function. Proteinuria is present but usually at levels of < 2 g/day in progressive hypertensive nephrosclerosis. However, proteinuria can reach nephrotic ranges (> 3.5 g/day) in patients with malignant hypertension or poorly controlled BP.[43]

Some argue that primary hypertension is an overstated cause of kidney failure.[44–46] By contrast, the AASK pilot study identified arteriolar and/or arterionephrosclerosis as the primary lesion in all 39 kidney biopsies from patients with proteinuria (< 2.5 g/day); there was no history of diabetes or other cause of primary kidney disease.[47]

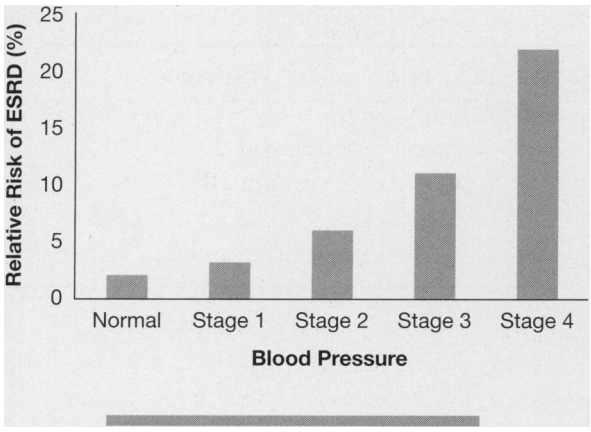

Figure 2. Increase in the Risk of ESRD with Increasing Blood Pressure, as Assessed by JNC 5 Criteria.[40] *Data from Klag et al. 1996.*

Lessons from the AASK Study

A large number of clinical trials have demonstrated that treatments that reduce proteinuria can slow decline in kidney function, mostly among diabetic patients.[48,49] More recently, a number of clinical trials in people with non-diabetic kidney disease, including the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) and Ramipril Efficacy In Nephropathy (REIN) trials, have shown that reduction in proteinuria with ACE inhibitors is associated with a delay in the time to doubling of serum creatinine concentrations and a decline in GFR.[36,50] Moreover, data from long-term clinical trials, such as AASK, demonstrate that failing to reduce proteinuria, in spite of BP reduction, while not directly harmful, does not provide optimal preservation of kidney function.[51]

ACE inhibitors have been the most effective agents to reduce proteinuria, although they have not always been thought to be the most effective anti-hypertensive agents in African Americans (Table 4).[52,53] However, this latter theory has been refuted by several studies, most notably the AASK study. Diuretics and calcium channel blockers (CCBs) have been touted as the more effective BP medications in this patient population; however, dihydropyridine CCBs are less renoprotective than ACE inhibitors.

The AASK study examined the impact of anti-hypertensive therapy on the progression of kidney disease in people with hypertensive kidney disease. The key findings from this study are outlined below.

1. The presence of mild kidney insufficiency does not prevent attainment of the target BP < 140/90 mmHg (as confirmed in the Hypertension Optimal Treatment [HOT] trial) but does require multidrug therapy (Table 4).

2. ACE inhibitor therapy is as effective in lowering BP as CCB therapy in African Americans with hypertensive kidney disease when used in multi-drug regimens—both required the same number of additional drugs, with diuretics being the most widely used second agent.

Table 3. Clinical Features of Hypertensive Nephrosclerosis

- Proteinuria (< 2.5 g/day)
- No other etiology for kidney disease
- Long-standing or severe hypertension with an onset of hypertension prior to the development of proteinuria or an increase in serum creatinine
- Evidence of other target organ damage such as retinopathy, and/or left ventricular hypertrophy
- Increased prevalence among African Americans
- Family history of hypertension
- Onset of hypertension at 25 to 45 years of age
- Renal biopsy demonstrating hyalinization of arterioles and fibroplastic intimal thickening of small arteries, glomerular ischemia and interstitial fibrosis

3. ACE inhibitor therapy provided more renal protection than CCB-based therapy in patients with > 300 mg/dL proteinuria (and perhaps among those with lesser amounts).

4. The degree of proteinuria, as well as the degree of elevation of serum creatinine is predictive of the rate of loss of GFR in hypertensive nephrosclerosis.[51]

Table 4. Average Number of Anti-hypertensive Agents Used to Achieve Target Blood Pressure (BP)

	MDRD[54]	ABCD[55,56]	HOT[57]	UKPDS[58]
Target BP	< 92 mmHg MAP*	< 75 mmHg DBP	< 80 mmHg DBP	< 85 mmHg DBP
Achieved BP	93	~75	81	82
Average number of drugs/patient	3.6	2.7	3.3	2.8

MDRD = Modification of Diet in Renal Disease.
ABCD = Appropriate Blood Pressure Control in Diabetes.
HOT = Hypertension Optimal Treatment.
UKPDS = United Kingdom Prospective Diabetes Study.
DBP = Diastolic Blood Pressure.

*The goal mean arterial pressure (MAP) of < 92 mmHg specified in the MDRD trial corresponds to a systolic/diastolic blood pressure of approximately 125/75 mmHg.

CONCLUSIONS

Multifaceted intervention programs aimed at delaying and preventing diabetic nephropathy using measures, such as screening, prevention, and the optimal treatment of hypertension and diabetes, are essential in the management of ESRD. Lifestyle modifications are particularly important in African-American populations as they are at high risk of developing kidney disease because of increased social, environmental, and genetic factors, such as obesity, hypertension, cigarette smoking, and type 2 diabetes, as well as heightened responsiveness to increased salt intake. Screening and prevention programs need to be combined with initiatives in other areas, such as educational programs, improved access to healthcare, and policy changes to address societal issues and reimbursement.

In some instances, hypertensive nephrosclerosis and diabetic nephropathy may progress to ESRD despite aggressive BP and blood glucose control and renoprotective anti-hypertensive medications. Thus, it is necessary to intervene before hypertension or diabetes cause established kidney damage. Results from the AASK study have confirmed previous findings from patients with diabetic nephropathy or other proteinuric states that blockade of the RAAS is beneficial in slowing kidney disease progression, although the evidence is less conclusive for patients with hypertension and proteinuria < 300 mg/dL, a subgroup at lower risk for progressive kidney disease. Because of the overall high risk of kidney disease in African Americans, it is particularly important to treat hypertension to JNC 5 criteria and to treat albuminuria aggressively. Thus, measurement of urinary protein excretion is recommended to guide initial drug therapy. Results from the RENAAL and IDNT studies indicated that the angiotensin receptor antagonists can be used effectively in African Americans with hypertension, obesity, and type 2 diabetic nephropathy to delay the progression of the disease.

Micro- or macroalbuminuria and/or minimally elevated serum creatinine concentrations are not only markers of kidney disease but are also powerful predictors of cardiovascular events. Thus, if albuminuria is not detected or aggressively treated in the hypertensive and diabetic populations, progression of kidney disease and more cardiovascular events are likely to occur. Anti-proteinuric effects of ACE inhibitors in hypertensive individuals can be seen at 3 months, and therapy should be titrated to achieve at least a 50% reduction in baseline proteinuria. It is uncertain whether anti-hypertensive agents that do not reduce proteinuria, if used with agents that can decrease proteinuria, will preserve kidney function to the same degree as agents that routinely decrease urinary albumin excretion.

The association of salt sensitivity with hypertension, together with higher rates of target organ damage, are important issues in African Americans, and suggest that anti-hypertensive therapy should include salt restriction as well as diuretic therapy for both adequate BP control and renal protection. In addition, obesity in African Americans should be addressed and every effort made to minimize the risk of developing insulin resistance, which may progress to overt diabetes, with its associated organ complications, particularly CKD.

The dramatic increase in the incidence of ESRD in the US is particularly evident among African-American populations. A concerted effort among clinicians is necessary to raise awareness in the communities most affected, to provide them with strategies for prevention and, ultimately, limit the rate of growth in cases of kidney failure. Targeting hypertension and diabetes offers unique opportunities to address critical factors in over 75% of the emerging ESRD population.

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