Diabetic Nephropathy in African Americans

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Diabetic nephropathy (DN) is the number one cause of end-stage renal disease in United States and is highly prevalent in African Americans. We have found that among African Americans in Mississippi diabetic nephropathy appears to affect females more than males, which may be related to increased rates of obesity and diabetes in African American women. Glycemic control and control of blood pressure is essential to prolong renal survival and to protect against cardiovascular events. Angiotensin-converting enzyme inhibitors reduce cardiovascular mortality in diabetics and are tolerated in advanced renal disease. The impact of glycemic control, appropriate antihypertensives, and the optimal level of blood pressure control in African Americans with advanced DN require further study. This article reviews the impact, clinical characteristics, risk factors, and treatment of diabetic nephropathy in African Americans. Am J Hypertens 2001; 14:132S–138S © 2001 American Journal of Hypertension, Ltd.

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Type 2 diabetes mellitus is 1.4 to 2.2 times more prevalent in African Americans compared with whites.1 The financial impact of the disease is enormous and becomes all the more staggering when one considers days lost from work for those with the disease and their caretakers. This effect of diabetes predominantly results from the microvascular complications that are also more severe in minority populations.1

African Americans have consistently suffered from over 3.5-fold higher rates of end-stage renal disease (ESRD) compared with whites. The rates of ESRD from hypertension, diabetes, and glomerulopathic causes are all substantially higher in African Americans compared with whites.2–4 Until recently, the excess of ESRD in African Americans was believed to be due to hypertension; however, the impact of diabetes (especially Type 2) in African Americans is so significant that it has been suggested that diabetes may now be responsible for the excess of ESRD seen in African Americans.4 Diabetic nephropathy (DN) is now the number one cause of ESRD in the United States and in African Americans.2 In addition, the risk of ESRD from any cause is increased ninefold in diabetic men compared with nondiabetic men.3 This article reviews several issues regarding diabetic nephropathy with an emphasis on information (where available) on African Americans.

Epidemiology

In the early 1980s DN accounted for just over 20% of all ESRD. The incidence has steadily increased such that over 40% of new ESRD starts in 1997 were due to DN.2,5 Hispanic Americans, Native Americans, and African Americans all have rates of DN that are higher than seen in whites, which is not explained by the higher rates of diabetes in these groups.2 For example, compared with whites, African Americans with diabetes have a 3.2–6.6-fold increase in risk for ESRD that remains two- to threefold higher when adjusted for the increased prevalence of diabetes in the African American community. Among African Americans most DN is seen in Type 2 diabetics,1,2 as Type 1 diabetes has a relatively low prevalence in this population. In comparison, significantly more whites with DN will be Type 1 diabetics, although Type 2 diabetes now accounts for the majority of DN in this group also.2

Hypertension is still an important cause of ESRD in African Americans and is disproportionately higher in African Americans compared with whites. We have observed that among African Americans the frequency of DN or hypertension as a cause of ESRD varies significantly with gender.6 In a retrospective study of patients that entered the ESRD program through our medical center from 1993 to 1998, we observed that DN was the cause of ESRD in 50.5% of African American females. However, among African American males, hypertension was the primary cause of ESRD (48.1%), with only 17.6% due to DN. Hypertension was the cause of ESRD in only 18.7% of African American women.6 Nationally, this difference in rates of ESRD owing to DN in African Amer-
ican men and women is not as substantial. This difference may be due to the increased prevalence and incidence of diabetes and obesity among African Americans in Mississippi and the United States. However, the difference in incidence of new Type 2 diabetes between African American men and women in Mississippi does not account for the difference in rates of DN.

Most epidemiologic studies in DN have concentrated on ESRD. Much less is known about rates of nephropathy earlier in the course of diabetes. This is partly because many Type 2 diabetics are undiagnosed (~50%) or are not identified by population studies that recognize only those receiving medical therapy for diabetes as having the disease. In a study of older urban adults in a geriatrics clinic (~80 years mean age), diabetes occurred in 21% of African Americans compared with 11% of whites and 29% of Hispanics. DN was present in one-third of diabetic patients and was more prevalent in older African Americans than whites.

Similar to what has been seen with hypertension in the United States, there is an increased risk of declining renal function in African Americans with diabetes compared with whites. Data from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that among diabetic adults African Americans are three times more likely to have early declines in renal function compared with whites. Declines in renal function by year 3 (defined as an increase of >0.4 mg/dL in creatinine (Cr)) among diabetic adults with normal Cr at baseline was more likely in African Americans. The increased risk for early renal decline was explained by differences in modifiable factors such as blood pressure, glucose, education, and income. Variations in genes, rates and severity of hypertension, obesity, and barriers to education and health care are factors postulated as a potential cause for the discrepancy in rates of DN and renal decline between African Americans and whites. However, even after adjusting for factors such as hypertension, glycemic control, and increased rates of diabetes in African American communities, the rates for ESRD resulting from DN are still over 60% higher than in whites.

**Clinical Characteristics**

Diabetic nephropathy is characterized by the appearance of albumin in the urine that progresses to overt proteinuria. Nephropathy usually develops after 10 to 15 years of diabetes. In the early stages of disease, hyperfiltration, changes in renal hemodynamics, and various pathologic changes may occur. Pathologically, DN is characterized by the accumulation of extracellular matrix (ECM) proteins in the glomerulus and is represented morphologically by thickening and expansion of the glomerular basement membrane and the mesangium. With poor glycemic control and arterial hypertension renal function declines in a significant proportion of diabetics, which is associated with glucose and hypertension enhanced synthesis and accumulation of mesangial ECM. To date, there is no documentation that the lesion of DN is significantly different in African Americans compared with other groups.

Hyperfiltration, which can be seen early in DN, has been postulated to be an important factor in DN and has been used as a marker for early DN. The role of hyperfiltration has received the most attention in whites with Type 1 diabetes; however, studies examining hyperfiltration in African American diabetics have been performed. One study found hyperfiltration as defined by a glomerular filtration rate (GFR) >140 mL/min was present in 36% of African Americans with early Type 2 diabetes (duration of <1 year). Hyperfiltration was more likely to be present in younger patients who did not have albuminuria, but its presence was not associated with an increased risk of developing renal impairment. They concluded that hyperfiltration does not predict renal decline in African American Type 2 diabetics.

Another early sign of DN is the presence of microalbuminuria. Diagnosis of microalbuminuria is important, as once overt DN, manifesting as persistent proteinuria, is present it is possible only to slow but not halt the progression toward ESRD. Microalbuminuria has been shown to be present in several diabetics and is an independent risk factor for decline of renal function. Its role as a predictor rather than merely a marker of disease is debatable. However, it has been shown that intervention—typically with control of blood pressure—can lead to resolution of microalbuminuria in early DN and conceivably halt disease progression.

Albuminuria is present in 30% to 40% of African Americans diabetic, and some studies have shown it to be present in the first year of diabetes. The presence of albuminuria in African Americans is associated with blood pressure, duration of diabetes, lipids, male gender, and fasting blood sugar. Microalbuminuria may resolve in many Type 1 diabetics with glycemic and blood pressure control, but this resolution of microalbuminuria is less likely to occur in Type 2 diabetics. As a group, African Americans with DN often present late in their course and have worse glycemic and blood pressure control, therefore, in African Americans resolution of microalbuminuria would be less likely.

**Factors in Disease Development and Progression**

As mentioned above, African Americans with diabetes are at increased risk for decline in renal function and development of ESRD. It is not completely understood why this is the case, but several factors have been implicated. Specifically, hypertension, poor glycemic and lipid control, obesity, genetics, low birth weight, and decreased access to health care all have received attention as factors contributing to this problem. Although it is generally agreed that hypertension significantly contributes to this
higher risk for renal decline, data on the role of the other factors are either lacking or not consistent.

The role of hypertension in renal disease has been clearly defined in both diabetics and nondiabetics and its role in African Americans with DN is important. Tierney et al showed that Type 2 diabetes, systolic hypertension, and African American race were major risk factors in the development and perpetuation of renal failure. Similarly, proteinuria correlates with blood pressure and progression of renal disease and is seen more commonly in African Americans with diabetes compared with whites. In the Modification of Diet in Renal Disease (MDRD) study the level of proteinuria correlated with the blood pressure reduction required to slow the progression of renal disease in African Americans. Therefore, it appears that blood pressure control may be of relatively more importance in African Americans with DN than in other groups, but there are studies to the contrary.

Glycemic control has been shown to be associated with the risk of developing or progression of DN in Type 1 diabetics. The renal protective effects of glycemic control in DN are most evident early in the course of disease when Cr is normal or near normal. Despite evidence that glycemic control is important, glucose control is poor in the United States in general and is worse in minorities. How glycemic control and blood pressure regulate the development and progression of DN has received considerable attention, but most of this work has been performed in animal models. There are numerous autocrine/paracrine growth factors that mediate the cellular alterations seen in DN, such as transforming growth factor β (TGF-β) and angiotensin II (ANG II). Many factors that mediate DN are regulated by glucose and arterial hypertension through processes such as nonenzymatic protein glycation, cellular sensing pathways such as the hexosamine biosynthesis pathway, effects on the vessel wall, or through alterations in cellular signaling pathways.

Whether the increase in DN and the higher likelihood of disease progression seen in African Americans are related to some alterations in these cellular processes is not known. However, net renal production of TGF-β1 is increased in Type 2 diabetics compared with nondiabetics, and circulating levels of TGF-β1 are increased in African Americans with ESRD compared with whites. In Type 1 diabetics with DN, TGF-β1 level decreased with captopril treatment and this was correlated with changes in GFR. Future studies that focus on the cellular processes mediating DN in African Americans will be needed to effectively devise therapies targeted at this population and to better identify those at higher risk of renal decline.

The data for glycemic control contributing to the prevention of and slowing progression of microvascular complications of diabetes in Type 2 diabetics are not as compelling as they are in Type 1 diabetes. However, there are suggestions that it may be of some benefit in Type 2 diabetics, but with regard to DN specifically, blood pressure control is likely to be more important. Although albuminuria correlates with fasting blood glucose, the role of glycemic control in African Americans with DN is not clear. For example, in a study of over 250 Mexican Americans, African Americans, and whites with diabetes, glycemic control and blood pressure were not predictors of renal decline. Being Mexican American and female correlated with the highest rates of renal decline, whereas increasing age, duration of diabetes, and duration of hypertension were associated with a slower rate. The authors concluded that ethnicity- and gender-related factors may be as strong as blood pressure and glycemic control in the course of DN in Type 2 diabetics.

Results from studies such as the one mentioned above indicate that, like whites, some minority diabetic patients are more prone to development of progressive DN than others. Combining this observation with the fact that African Americans have increased rates of DN compared with whites has led many to hypothesize that there are genetic factors at play. This is supported by several studies showing an association between a family history of ESRD and increased risk of ESRD. This association may be stronger in African Americans than whites, and this clustering of ESRD in families is higher than predicted by the clustering of diabetes and hypertension in these groups.

Further support of the theory that genetics has a role in determining who develops DN and has disease progression is the fact that DN is more common among those diabetics who have a first-degree relative with DN. Similarly, diabetes itself is observed with high frequency among relatives of ESRD patients who have hypertension as their primary ESRD diagnosis although the probands in this study did not have diabetes. Factors that are predictive of progression of DN are also heritable. For example, urinary albumin excretion has been demonstrated to be a heritable trait and genetically correlated to blood pressure in white families with Type 2 diabetes.

Several genes have been examined for an association with DN, proteinuria, hypertension, and other renal diseases. Some studies have demonstrated association of some genes with progression of and markers of DN. For example, in African American females with gestational diabetes it was observed that genes within the flanking region of the major histocompatibility region were risk factors for microalbuminuria, diabetes, insulin resistance, and hypertension. In addition, in Type 1 diabetics and nondiabetics the deletion polymorphism of the angiotensin-converting enzyme (ACE) gene is a predictor of more rapid renal decline. However, it is not associated with the development of microalbuminuria or proteinuria in diabetic renal disease. Although some genes are associated with progression of DN, no genetic variations have been conclusively shown to be causative of DN in African Americans. Yu et al examined genes for several of the components of the renin-angiotensin system (RAS), plasma kallikrein, and growth factors in African American sib pairs with ESRD due to diabetic and nondiabetic renal
disease. They found no linkage of any of these in vitro mediators of DN with the disease.39–41

Other factors implicated as contributing to the progression of DN are lipids, obesity, and low birth weight. Among Type 1 diabetics hyperlipidemia may be a risk factor for progression of renal disease, and there have been suggestions that obesity may independently increase albuminuria.5 The role of obesity in DN among African Americans is important, as obesity is a significant contributor to the increased rates of diabetes seen in this group.1,7 Low birth weight has been hypothesized to contribute to renal disease through its association with decreased nephron number and hypertension later in life. For example, in European Type 1 diabetics, females in the 10th percentile of birth weight were more likely to have nephropathy than those in the 90th percentile.42 In addition, fetal undernutrition has been suggested as a factor for increased rates of Type 2 diabetes seen in youth,43 an entity seen increasingly in minority populations. The role of low birth weight as a cause or predictor of DN in African Americans requires further study.

**Therapy**

Although the most important measure in DN in African Americans is prevention, attention must be paid to those with the disease. As mentioned above, the most important intervention in people with DN is blood pressure and glycemic control, and early intervention is advised. The current recommendation for target blood pressure in DN is 130/80 mm Hg.29,44–46 The benefit of blood pressure control is, in large part, independent of the choice of antihypertensive agent. This was demonstrated several years ago in studies in Type 1 diabetics treated with varying blood pressure–lowering agents.45 With lowering of blood pressure there was a decline in the rate of renal decline and lowering of proteinuria.44 It has been suggested that there is no J-curve phenomenon with regard to blood pressure and preservation of renal function in DN. However, we have observed a worsening in renal survival among African Americans with advanced DN and mean arterial blood pressure <100 mm Hg compared with those with higher blood pressure.45 This is not to say that blood pressure control is not important in people with advanced disease, as renal survival was also worse in those with a mean arterial pressure >110 mm Hg compared with those with lower pressures. What the optimal blood pressure is in the later stages of DN will require further study. We should recognize that what blood pressure is optimal for renal survival might not be appropriate for protection against cardiovascular disease in those with advanced DN.

The next question one has to consider is what agents are best to use to achieve blood pressure goals in DN. As mentioned above, the benefits of blood pressure control are often independent of the specific agent45; however, some antihypertensives have received particular attention in DN. Angiotensin converting enzyme inhibitors and calcium channel blockers (CCB) have received the most attention in DN and will be reviewed below. There are small studies that examine the response of African Americans with DN to various antihypertensive regimens. To date, there are insufficient data to support significant racial differences in treatment of blood pressure in DN. Similarly, there are no data to suggest that etiology of DN, and therefore response to antihypertensive therapy, is different among racial groups.

Clinical trials generally support a favorable effect of ACE inhibitors on proteinuria and progression of diabetic kidney disease.47–49 Similar results on proteinuria and renal function have been seen with angiotensin receptor blockers.50 It has been suggested that ACE inhibitors provide renal protection in DN that is in addition to their effects on blood pressure.47 However, this point is debatable, as most trials comparing ACE inhibitors with placebo or other agents have lower blood pressures in the ACE inhibitor group. Although the specific role of ACE inhibitors on renal survival in those with advanced DN is still not clear, there is strong support to have ACE inhibitors as part of the antihypertensive cocktail in all diabetics with micro- or macroalbuminuria.51 Perhaps the most substantial benefit of ACE inhibitors in diabetics is the cardiac protection they provide.51

There is concern regarding the safety and efficacy of ACE inhibitors in people with advanced renal disease. In fact, the effects of ACE inhibitors in patients with advanced diabetic and nondiabetic renal disease are mixed, but there are data to support their use in those with abnormal renal function. The Collaborative Study Group showed that the effects of ACE inhibition in Type 1 DN were most evident in those with serum creatinine over 1.5 mg/dL.47 Bakris and Weir demonstrated that Cr may increase by 30% within 2 months of ACE inhibitor administration. However, this increase in Cr was strongly associated with long-term stabilization of renal function and was present in those with Cr >1.4 mg/dL.52 We also noted tolerance of ACE inhibitors in African Americans with advanced DN (Cr >2.5 mg/dL).53

Whereas CCB are considered efficacious in African Americans,54 clinical trials examining the role of CCB in DN have produced varied results.46,55–57 Their effects on proteinuria and GFR are not uniform and vary according to type.46,55 In general, nondihydropyridine (NDH) CCB have more of a beneficial effect on the diabetic kidney than dihydropyridines.44,55 Finally, the effects of CCB on CVD and CVD mortality have been questioned in diabetics and nondiabetics and appear to be inferior to ACE inhibitors and β-blockers.51

Some studies have compared the effects of CCB, ACE inhibitors, and β-blockers in DN. In a study of 34 African Americans with Type 2 DN, verapamil was more effective than atenolol at slowing the rate of renal decline and decreasing proteinuria.58 In a similar study with African Americans with Type 2 DN, lisinopril, NDH CCB (verapamil or diltiazem) and atenolol were compared over 60 months. The
decline in renal function was greatest with atenolol. ACE inhibitors and CCB had similar effects on renal function and proteinuria. However, the role of β-blockers in DN in the UK Prospective Diabetes Study Group was favorable, as atenolol tended to be better than captopril in preventing macrovascular and microvascular complications.

Hypertension in people with DN usually results in significant elevations in blood pressure, and over 65% of patients with DN need at least two drugs to control blood pressure. Therefore, some studies have examined the combinations of antihypertensive regimens. The combination of ACE inhibitors and CCB may have synergistic effects on renal function by lowering proteinuria and protecting against renal injury. Similarly, in African Americans the effects of CCB on albuminuria are enhanced when dietary sodium is restricted.

We examined the effect of specific classes of antihypertensive agents in treating advanced DN in a retrospective study of predominantly African American ESRD patients with DN as their primary ESRD diagnosis. The average Cr at presentation to our nephrology clinic was almost 6 mg/dL in those patients. Renal survival was defined as the time from initial clinic visit to the initiation of renal replacement therapy. ACE inhibitors had no effect on renal survival in the total cohort. However, patients who presented to our clinic with a Cr ≤ 4.0 mg/dL had worse renal survival when they presented on an ACE inhibitor. The lack of benefit of ACE inhibitors in this group may be due to the poor blood pressure control. Those who presented on an ACE inhibitor had significantly higher blood pressures than those who were not receiving an ACE inhibitor. This supports the importance of the level of blood pressure control over choice of antihypertensive agent with regard to renal survival in African Americans with DN.

In that same cohort, we also examined the effects on CCB on renal survival. Presenting while receiving a CCB was a negative predictor of renal survival among African Americans, which was not dependent on differences in serum creatinine. In fact, patients not receiving a CCB at presentation had higher Cr than those receiving a CCB at presentation. It is clear that larger prospective trials are needed to determine the role of specific antihypertensives in African Americans with advanced DN. Fortunately, some of these questions will be answered in the African American Study of Kidney Disease.

Treatment of ESRD in Diabetic Nephropathy

The optimal treatment for ESRD is renal transplantation. Wolfe et al demonstrated that patients who are well enough to be placed on the waiting list for renal transplantation have about a 68% reduction in the long-term risk of death once they receive a kidney. In all age groups a more substantial impact of transplantation was seen in diabetics compared with nondiabetics. With transplantation the mortality of diabetics with ESRD improves. However, mortality is still high in this population because it only becomes equivalent to and does not exceed the survival of nondiabetics with ESRD on dialysis. Transplantation is beneficial in African Americans with DN. Unfortunately, fewer African Americans are referred for transplantation, and survival in African Americans is not as good as whites after transplantation.

Summary

Diabetes and DN are highly prevalent in African Americans, and DN is now the number one cause of ESRD in this population. Several factors have been hypothesized to cause the increased rate of DN in African Americans compared with whites, and the cause of this discrepancy appears to be multifactorial. Among African Americans DN is more frequent in females, which may be due to the increased rates of obesity and diabetes seen in African-American women. Blood pressure control is important in prevention of and development of DN, but the specific level of blood pressure control and which agents are optimal to achieve these goals in people with advanced DN will require further study. Finally, it will be important to study the cellular processes mediating DN in African Americans specifically, so that those at high risk can be readily identified and treated preventively.

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References