Advanced Diabetic Nephropathy Disproportionately Affects African-American Females: Cross-Sectional Analysis and Determinants of Renal Survival in an Academic Renal Clinic

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Objective: The aims of this study were to study further the previously observed 2-fold higher prevalence of endstage renal disease (ESRD) due to diabetic nephropathy (DN) in African-American (AA) women, when compared to AA men, and to identify factors predictive of renal survival in this population.

Design: Cross-sectional analysis of DN in an academic renal clinic.

Methods: We identified and retrospectively studied all patients with diabetic nephropathy enrolled in our renal clinic in 1996. Charts were reviewed for basic demographic factors, medications, and renal function.

Results: Of ~600 total patients, 141 were diagnosed with DN, and sufficient data was available on 119 (98 AA) of these, with a mean followup of 105 weeks. Patients were hypertensive, had advanced renal disease at presentation (creatinine [Cr]=3.97 mg/dL), and had been diabetic for 16.7 years. The AAs were disproportionately represented by females (69 vs 29). Seventy patients reached ESRD at the time of analysis (April 2000) with a mean time to dialysis of 79.3 weeks. Significant determinants for longer time to ESRD (TTE) were: lower presenting Cr, female gender, and AA race. A MAP<100 mm Hg over the course of followup was adversely related to TTE. Among AAs, taking an angiotensin converting enzyme (ACE) inhibitor, or a calcium channel blocker, was associated with better renal survival. Changes in renal function at 1 and 2 years were associated with age, urine protein at presentation, and MAP over the course of followup.

Conclusions: In Mississippi, DN is more much more prevalent in AA females, compared to AA males. In those with advanced DN, MAP<100 mm Hg may lessen the chances for renal survival. (*Ethn. Dis.* 2003;13:28–33)

Key Words: Diabetic Nephropathy, African American, Hypertension, Endstage Renal Disease, Angiotensin Converting Enzyme Inhibitor, Female Gender

Introduction

Diabetic nephropathy (DN) is the number one cause of end stage renal disease (ESRD) in the United States.[1,2] Previous work from our group demonstrated that African-American females were much more likely to have DN as their primary ESRD diagnosis, compared to African-American males.[3] This prior, retrospective study examined factors affecting renal survival among patients who developed ESRD, secondary to DN, from 1993 through 1998, inclusive. Over 80% of those studied were African-American. DN was the diagnosis for 50.5% of ESRD cases among African-American females. However, DN accounted for only 17.6% of ESRD cases among African-American males. In contrast, hypertension was the primary ESRD diagnosis in 48.1% of African-American males, and only in 18.7% of African-American females.[3]

While clinical trials generally support a favorable effect of angiotensin-converting enzyme (ACE) inhibitors on proteinuria and progression of diabetic kidney disease,[4–6] these agents did not prolong renal survival in this earlier ESRD study.[3] Studies in type 1 and 2 diabetics with DN have demonstrated that blood pressure control may be the most important determinant in the rate of progression of kidney disease in diabetics.[7–9] We observed that blood pressure control was a predictor of renal survival; however, this was the first study of diabetic renal disease in which a J-curve phenomenon was observed. The lack of a beneficial effect of ACE inhibitors, and the presence of the J-curve phenomenon, may be explained by the advanced renal disease with which our patients presented, and by their poor blood pressure control.

Selection bias is inherent in a study that selects only patients who have reached ESRD. For example, one possible explanation for the greater impact of DN in African-American females, when compared to males, is that African-American males with diabetic nephropathy do not reach ESRD. This could be due to a slower rate of renal disease progression among these patients, or to their dying from cardiovascular disease (CVD) prior to reaching ESRD. Similarly, any benefits of specific antihypertensive agents, such as ACE inhibitors, may be masked by selection of a group that was inadequately treated, or somehow resistant to therapy. Therefore, we carried out a cross-sectional analysis in which we identified all patients with diabetic nephropathy enrolled in our renal clinic in 1996; 4 years later, we retrospectively studied this cohort. The roles of several factors, including blood pressure control and specific antihypertensive agents, on renal survival were examined. We hypothesized that those with better blood pressure control, and who were taking an ACE inhibitor, would have better renal survival. In addition, we postulated that the discrepancy in impact of DN among African-American females compared to males would not be as significant as seen in the ESRD study. We demonstrate that DN in African Americans in Mississippi is predominantly a disease of the obese African-American female, and that there may be a narrow therapeutic

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Studies in type 1 and 2 diabetics with DN have demonstrated that blood pressure control may be the most important determinant in the rate of progression of kidney disease in diabetics.[7–9]

window for blood pressure control in those with advanced disease.

METHODS

Patients

In January–March 1997, the 1996 schedules for the renal clinic of the University of Mississippi Medical Center (UMMC) were reviewed. Pre-ESRD patients, with a diagnosis of diabetic nephropathy, were selected for analysis. A total of 703 individuals were scheduled for visits during that calendar year, 56 of whom never presented to the clinic, and 30 of whom already had ESRD. Of the 617 pre-ESRD patients who presented to the clinic in 1996, 141 were diagnosed with diabetic nephropathy. Sufficient data were available on 119 patients, and are reported here.

Data

The hospital and renal clinic charts of the 119 patients entered into the study were reviewed. For this study, we began our analysis with the initial presentation to a UMMC nephrologist. The following data was extracted from charts on, or around, the date of the first visit: age, sex, race, systolic and diastolic blood pressures (SBP, DBP), weight, height, blood urea nitrogen (BUN), creatinine (Cr), duration of diabetes, type of diabetes, urine protein excretion, creatinine clearance (CrCl, by 24-hour urine collection), presence of retinopathy, and use of blood pressure medications. The chart was then reviewed for blood pressure measurements over the course of followup, as well as for changes in antihypertensive medication, and changes in renal function. Antihypertensive medications were classified by groups (ACE inhibitors, calcium channel blockers (CCB), diuretics, centrally acting agents, vasodilators, β-blockers). The mean arterial blood pressure (MAP) was determined for each follow-up visit. The mean MAP over the course of followup (follow-up MAP) was determined in those with at least one blood pressure measurement at ≥3 months of followup. Data was extracted in April–May 2000. The endpoint was the patient's entrance into the ESRD program, or the last clinic visit prior to the date of data extraction.

Analysis

Renal survival was expressed as the change in 1/Cr at years 1, 2, and 3. Because there were relatively few patients with at least one year of followup (N=68), we also looked at the time to ESRD (TTE) as a measure of renal survival. TTE is the time from the initial presentation to a UMMC nephrologist until the patient's entry into the ESRD program. In analysis using TTE as an endpoint, data from those not reaching ESRD were censored. Data were entered into the STATVIEW (Abacus®) program for analysis. Univariate and multivariate proportional hazards regression analyses (Cox [proportional hazards] model) were used to identify factors significantly correlated with renal survival. Factors entered into analysis were: age; gender; race; type of diabetes; duration of diabetes; initial SBP; initial DBP; initial BUN; initial Cr; body mass index (BMI); presenting on an ACE inhibitor; presenting on a CCB; the number of blood pressure medicines taken at presentation; starting an ACE inhibitor at renal clinic; starting a CCB at renal clinic; ever taking an ACE inhibitor; ever taking a CCB; follow-up MAP (as continuous variable); and follow-up MAP <100, 105, or 110 mm Hg. Factors found to be significant on univariate analysis were entered into multivariate analysis. Hazards ratios are given with confidence intervals. Values between groups were compared by t test. A P value of <.05 was considered significant.

RESULTS

The characteristics of the 119 patients entered into the study are shown in Table 1. In general, patients were obese, hypertensive, had advanced renal disease at presentation, and had been diabetic for several years. The advanced state of renal disease was demonstrated by the fact that only 68 patients had at least one year of followup. Seventy (58.8%) patients reached ESRD, with a mean time of 79.3 weeks from their first contact with a nephrologist. Ninety-eight (82.4%) of the patients were African-American. Sixty-nine (70.4%) of the African Americans were female, once again demonstrating that DN may have more impact on African-American women than men.

Factors Affecting Renal Survival

Initially, we examined the factors that determined renal survival among the entire cohort. We used the changes in the inverse creatinine at years 1, 2, and 3, of followup as a measure of change in renal function. Univariate analysis factors significantly related to worse odds for renal survival (increased delta 1/Cr) at year one (N=68) were older age, elevated initial Cr, and having a follow-up MAP <100 mm Hg (Table 2). Unexpectedly, when used as a continuous variable in this model, higher 24-urine protein excretion was associated with a lower delta 1/Cr at year one. On multivariate analysis, only the initial Cr and the 24-hour urine protein re-

Table 1. Characteristics of patient population (at initial clinic visit)

Patients (African-American)	119 (98)
Male/female	37/82
Age	55.7 ± 1.07 years
Type 1/type 2 diabetes	11/108
Duration of diabetes	16.7 ± .87 years
BUN	46.1 ± 2.6 mg/dl
Creatinine	3.97 ± .26 mg/dl
Systolic BP	156.8 ± 2.6 mm Hg
Diastolic BP	86.5 ± 1.3 mm Hg
Body mass index	33.2 ± .86 kg/m^2
24 hour urine protein	4.67 ± .49 grams
CrCl (by 24 hour urine)	36.5 ± 3.4 ml/min
# of antihypertensives at presentation	1.98 ± .1
# on ACE inhibitor at presentation	52 (44%)
# on CCB at presentation	51 (43%)
Average MAP over follow-up	109.2 ± 1.06 mm Hg
# reaching ESRD	70
Time to ESRD	79.3 ± 8.2 weeks
Mean follow-up	105.0 ± 11.7 weeks

BP=blood pressure; CrCl=creatinine clearance; ACE=angiotensin converting enzyme; CCB=calcium channel blocker; MAP=mean arterial pressure.

mained significant. Similarly, the initial Cr was the only significant determinant of delta 1/Cr at year 2 (N=36), and at year 3 (N=17), on both univariate and multivariate analyses.

The impact of proteinuria on renal survival was clearly exhibited by plotting urine protein against delta 1/Cr at year 1. In that case, a statistically significant positive correlation between these factors (r^2=.191, P=.0008, not shown) indicated that higher urinary protein excretion was associated with poorer odds of renal survival. In subsequent analysis, we divided the population into those with >3 grams of urine protein vs those with lower amounts. The delta 1/Cr was significantly higher among those with 24-hour urine protein >3 gm when compared to those with lower amounts (P=.0119). TTE tended to be less in those with >3 grams of urine protein (71.5 ± 9.7 vs 111.1 ± 20 weeks, respectively, P=.068). No significant difference in initial serum Cr was observed between the 2 groups.

The patients who reached ESRD were analyzed separately. Univariate analysis demonstrated that significant determinants of longer TTE were lower initial BUN and Cr, higher CrCl, female gender, African-American race, and follow-up MAP >100 mm Hg (Table 3). Multivariate analysis found only initial Cr and CrCl to be significant.

Subsequently, we analyzed African Americans as a group. African-American females were more obese than African-American males (BMI 35.2 vs 30.8 kg/m^2, respectively, P=.041), presented with a lower serum Cr (3.61 vs 4.87 mg/dL, P=.04), and tended to be older (57 vs 52.8 yrs, P=ns). With respect to delta 1/Cr at year 1, results were similar to those in the total cohort, except that follow-up MAP <100 mm Hg remained significant on multivariate analysis. Among AAs who reached ESRD, we observed that having taken an ACE inhibitor or calcium antagonist at any time was associated with improved odds of renal survival (Table 4). On multivariate analysis, only the initial serum Cr was significant. However, follow-up MAP <100 mm Hg tended to be a negative predictor of renal survival.

Table 2. Factors significantly related to delta 1/Cr at one year of follow-up

Factor	Confidence Intervals			
	Hazard Ratio	Lower Limit	Upper Limit	*P* Value
Univariate analysis (N = 68):				
Age	1.027	1.03	1.52	.0278
Initial Creatinine	2.024	1.61	2.54	<.0001
24-hour urine protein	.910	.844	.981	.0135
Follow-up MAP <100 mm Hg (yes)	5.73	1.9	17.3	.002
Follow-up MAP <105 mm Hg (yes)	2.13	1.11	4.08	.0223
Multivariate Analysis:				
Initial creatinine	2.41	1.76	3.3	<.0001
24-hour urine protein	.873	.746	.958	.004

See methods for list of factors entered into univariate analysis.

DISCUSSION

DN is the number one cause of ESRD, and its impact is increasing along with rising global rates of diabetes.[1,2] Our previous experience with ESRD secondary to DN was in an academic renal clinic, with a predominantly African-American population.[3] Notable findings in that study were that DN was much more likely to be the cause of ESRD in African-American females (~50%) than in AA males (<20%). In addition, ACE inhibitors were under-utilized, and lower blood pressure (MAP <100 mm Hg) was associated with poorer chances of renal survival.[3] To avoid selection bias, we performed a cross selection analysis of the patients with DN in that renal clinic. Again, most presented to a nephrologist late in the course of their disease, were hypertensive and obese, and were unlikely to be taking an ACE inhibitor.

Table 3. Factors related to time to ESRD (*N*=70)

Factor	Confidence Intervals			
	Hazard Ratio	Lower Limit	Upper Limit	*P* Value
Univariate Analysis (important factors):				
Gender (female)	.611	.355	1.05	.076
Race (African-American)	.552	.278	1.10	.0899
Initial creatinine	1.16	1.07	1.27	.0007
Initial BUN	1.02	1.01	1.03	.0004
CrCl	.978	.962	.993	.0057
Follow-up MAP <100 mm Hg (yes)	3.21	1.62	6.39	.0008
Multivariate Analysis:				
Initial creatinine	1.31	1.03	1.68	.0298
CrCl	.983	.968	.998	.0263

See methods for list of factors entered into univariate analysis. Only factors that were significant on univariate analysis (*P*<.05) were entered into multivariate analysis.

As before, we found that African-American females experienced significantly more DN than African-American males. While blood pressure and race were correlated with renal survival, the initial serum creatinine was the single most important determinant of renal survival.

A possible explanation for the significantly greater prevalence of DN among African-American females, when compared to AA males, is that more African-American females are diabetic. Data from the Atherosclerosis Risk in Communities Study (ARIC) has demonstrated that the incidence of type 2 diabetes is higher in African-American women, when compared to either African-American males, or all Caucasians.[10] This increased incidence in African-American females is attributed to the excess obesity and overweight in that population.[10] The ARIC data are important to the current study because the cohort studied was composed entirely of African Americans from Jackson, Mississippi. In ARIC, the difference in incidence of type 2 diabetes between African-American men and women in Mississippi, is not large enough[10] to explain the difference in rates of DN seen here and previously.[3]

There are several other possible reasons for the observed differences in ESRD due to DN among African-American men and women in Mississippi. The current study examined the hypothesis that African-American males with DN do not reach ESRD, either because of preserved renal function, or because of CVD mortality prior to reaching ESRD. However, this cross-sectional analysis demonstrated that African-American women still outnumbered African-American men, by nearly 2 to 1. In addition, the percentage of African-American males and females with DN who reached ESRD was similar (58.6% vs 62.3%, respectively). Therefore, if African-American males with diabetes are experiencing significant rates of cardiovascular events prior to developing ESRD, then these events would have to occur prior to the development of even moderate renal disease. Another argument against this hypothesis is found in NHANES data, which revealed an actual increase in age-adjusted heart disease mortality among diabetic females, vs a decrease in diabetic males.[11]

This increased incidence [of type 2 diabetes] in African-American females is attributed to the excess obesity and overweight in that population.[10]

Another possibility is that African-American men with diabetes develop DN at lesser rates than do diabetic African-American females. While this has not been specifically studied, contradictory data demonstrate that African-American males have an additional risk for development of elevated urine albumin to creatinine ratios.[12] In addition, US Renal Data System data does not reveal the >2-fold higher number of DN cases among African-American females, when compared to their male counterparts.[2] This cross-sectional analysis is not able to directly address this question, but ongoing prospective population-based studies among Mississippi's African Americans should provide opportunities to further explore this issue.[13,14]

We also examined the relationship between blood pressure and renal sur-

Table 4. Factors correlating with TTE for African Americans

Factor	Confidence Intervals			
	Hazard Ratio	Lower Limit	Upper Limit	*P* Value
Univariate Analysis (*N*=60):				
Initial creatinine	1.22	1.16	1.28	<.0001
CrCl	1.02	1.01	1.02	<.0001
ACE at any time (yes)	0.46	.262	.809	.007
Multivariate Analysis:				
Initial creatinine	1.23	1.13	1.34	<.0001
Follow-up MAP <100 mm Hg (yes)	2.72	.911	8.11	.073

vival in patients with advanced renal disease. Neither initial systolic, diastolic, nor mean arterial blood pressure, was significantly correlated with renal survival. However, as in our earlier study, we observed that follow-up MAP's effect on renal survival was such that those with a follow-up MAP <100 mm Hg had worse renal survival. In contrast to the earlier study, we did not observe an adverse effect of follow-up MAP >110 mm Hg on renal survival. This raises the question as to what blood pressure rates should be targeted in those with advanced DN. The current recommendation for target blood pressure in DN is <130/80 mm Hg.[15,16] Whether or not this target is "renal protective" in those with advanced disease, or in African Americans, in particular, will require further study. Until this question is specifically addressed in African-American populations, it is best to continue to use the current recommendation, as aggressive blood pressure control in diabetics has beneficial effects on cardiovascular disease.[17]

While the use of ACE inhibitors is generally recommended in DN,[4–6] many practitioners remain wary of prescribing them for those with advanced renal disease. ACE inhibitors have been demonstrated to be beneficial in advanced non-diabetic renal disease.[18] In addition, we have observed that ACE inhibitors are tolerated in African-American females with advanced DN (Cr >2.5 mg/dL).[19] In the current study, taking an ACE inhibitor or a calcium antagonist was associated with improved renal survival among African Americans who reached ESRD. More importantly, we did not observe the negative effects on renal function seen with both agents in the previous study.[3] This result is of practical importance, as this population requires multiple antihypertensive agents to reach their blood pressure goals.

Besides blood pressure and initial renal function, female gender, African-American race, and urine protein, were determinants of renal survival. In the analysis using the Cox [proportional hazards] model, elevated urine protein excretion was associated with a lower delta 1/Cr at year one. This unexpected finding is likely a result of the advanced disease seen in this population, the variability inherent is a 24-hour urine collection, and the selection bias of choosing patients for this urine collection. Only 82 patients were determined to have protein in their urine, with 44 of these patients having at least 3 grams in 24 hours. The average serum Cr of those without urine protein was significantly higher, compared with those who had it (5.14 ± .56 mg/dL vs 3.45 ± .25 mg/dL, P=.0019). Blood pressure may be another contributing factor to this variability, since those with >3 grams of proteinuria had higher follow-up MAP (113.2 ± 1.6 vs 108.7 ± 1.6, >3 grams vs lower, P=.045).

This study is limited by being retrospective, and because patients were not treated by a single protocol. Several different practitioners with varying styles treated patients; therefore, different criteria were applied for initiating renal replacement therapy. We do not have sufficient data to analyze the effects of other clinical factors,[1] such as glycemic control, dietary protein restriction, or serum lipid levels, on renal survival in this population. Finally, the use of delta 1/Cr is not as accurate as other methods for the assessment of renal function.[20] However, in a population such as this, with severe renal disease, the development of ESRD is the most important factor.

Despite these limitations, we are able to make some important observations. We demonstrate that African-American patients with DN presented to a nephrologist late in the course of their disease, had inadequate blood pressure control, and were often not taking an ACE inhibitor. Again, we observed a relatively narrow therapeutic window for blood pressure control in this population, with regard to renal survival. The study population included more than twice as many African-American females with DN as African-American males. Among African Americans, the rates of progression to ESRD do not differ between genders. Future research should attempt to determine the reason for these gender discrepancies, and to better understand which antihypertensive agents and levels of blood pressure are appropriate targets in this population. Finally, and most importantly, it is urgent that we identify the barriers to care in this population, so that preventive measures can be initiated in the early stages of the disease.

ACKNOWLEDGMENTS

EDC is the recipient of a career development award from the Veterans Administration. Part of this work was presented at the annual meeting of the International Society of Hypertension in Blacks, in Las Vegas, Nev., July 2001.

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