Contrasting Effects of Calcium Channel Blockade versus Converting Enzyme Inhibition on Proteinuria in African Americans with Non-Insulin-Dependent Diabetes Mellitus and Nephropathy

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Abstract. Hypertension is a common finding in non-insulin-dependent diabetes mellitus (NIDDM) nephropathy. African Americans have a high prevalence of NIDDM and hypertension, and are relatively resistant to the antihypertensive effects of converting enzyme inhibitors (CEI) but respond well to calcium channel blockers (CCB). In the long-term study presented here, the effects of isradipine, a dihydropyridine calcium antagonist, on the course of the nephropathy were investigated and compared with the effects of captopril in 31 African Americans with NIDDM and proteinuria (≥500 mg/day). The patients were stratified by levels of GFR and proteinuria, and they were randomized to receive isradipine (N = 16) or captopril (N = 15); doses were adjusted to maintain similar BP levels (<140/90). At 6 months, mean arterial pressure was similar (102 ± 3 and 104 ± 3 mm Hg in the isradipine and captopril groups, respectively) and GFR was unchanged (∆ = −4 ± 3 and +1 ± 3 ml/min/1.73 in the isradipine and captopril groups, respectively; P = NS). However, proteinuria in the isradipine group increased by approximately 50% (2.01 ± 0.40 versus 3.04 ± 0.70 mg/mg creatinine at baseline versus 6 months, respectively, P < 0.05), whereas captopril reduced proteinuria by 30% after 6 months (2.85 ± 0.70 at baseline versus 2.30 ± 0.70 mg/mg creatinine, P < 0.05). Dietary protein, sodium intake, and HbA1C levels were similar in both groups and did not differ from baseline. It was concluded that over 6 months, captopril reduces and isradipine increases proteinuria in African Americans with NIDDM and nephropathy. Whether this contrasting effect on proteinuria will result in different rates of progression is not known, but dihydropyridine CCB should be used cautiously in African Americans with diabetic nephropathy. (J Am Soc Nephrol 8: 793–798, 1997)

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States (1). Therapies reported to reduce proteinuria in diabetic nephropathy include treatment of hypertension (2–4), which has become the standard of care in the management of patients with insulin-dependent diabetes mellitus (IDDM). In animal models of diabetic nephropathy, both systemic and intraglomerular hypertension occur (5,6). The amelioration of injury by experimental approaches that selectively normalize intraglomerular pressure (5,7) suggests a predominant role for intraglomerular hypertension in the pathogenesis of progressive diabetic nephropathy.

The role of calcium channel blockers (CCB) in the treatment of diabetic nephropathy has not been established. CCB ameliorate glomerular injury in rats with hypertension, independently of normalization of intraglomerular pressure (8). In animals with streptozotocin-induced diabetes, CCB reduce systemic blood pressure but have variable effects on protein excretion and the degree of histologic damage (7,9,10). This variability is not well understood but has been attributed to differences among subclasses of CCB in affecting glomerular arteriolar tone (11,12). Besides their hemodynamic effects, CCB have other biologic effects of potential therapeutic use: they inhibit the proliferation of cultured human (13) and rat (14) mesangial cells, reduce the angiotensin II-mediated increase in mesangial trafficking of macromolecules (15), modulate glomerular hypertrophy in the remnant kidney model (8), and prevent mesangial and segmental glomerulosclerosis in streptozotocin-treated dogs (16). Because of these biologic effects and also because CCB have a favorable metabolic profile in diabetic patients (17) and are well tolerated, they are commonly used to treat hypertensive diabetic patients.

In African Americans, the prevalence of diabetes mellitus is approximately two times higher than in Caucasians. After adjusting for the increased prevalence of diabetes, diabetic ESRD is three to six times higher in African Americans than in whites (18). The responsiveness to different antihypertensive drugs is also affected by ethnic background; African Americans are relatively resistant to the systemic blood pressure-lowering effects of converting enzyme inhibitors (CEI) but are more sensitive to the systemic antihypertensive effects of di-

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uretics or CCB (19, 20). Whether there are similar differences in the response of intrarenal blood vessels is not known.

Recently, CEI have been shown to ameliorate progressive nephropathy in IDDM patients (21), presumably related to their ability to cause efferent arteriolar vasodilation and normalize intraglomerular pressure. Although both IDDM and non-insulin-dependent diabetes mellitus (NIDDM) have similar glomerular morphologic and pathophysiologic changes (22–25), differences between the two types of diabetes related to patient age, ethnicity, presence of comorbid conditions like obesity, and renovascular disease (26) could affect the outcome of therapy with different antihypertensive drugs.

The aim of our study was to determine the short-term effects of isradipine, a dihydropyridine CCB, on proteinuria and the course of the nephropathy of NIDDM in African Americans, and its relative effects on the rate of progression of the glomerular disease.

**Materials and Methods**

**Patient Population**

The study is a prospective, unblinded, randomized clinical trial performed at Grady Memorial Hospital in Atlanta. This hospital serves an inner-city population, mostly African Americans.

Patients with NIDDM attending the diabetes or renal clinics were screened for the presence of clinical proteinuria (urinary dipstick for protein >1+ or proteinuria >500 mg/day) and contacted to participate in a study approved by the Human Investigations Committee at Emory University. NIDDM was diagnosed based on clinical criteria: no episodes of diabetic ketoacidosis, initial response to diet alone or oral hypoglycemic agents, age >25 yr., and/or presence of obesity. Entry criteria were as follows: (1) age, 25–70 yr; (2) serum creatinine, <3.5 mg/dl, or creatinine clearance >25 ml/min; (3) proteinuria, >500 mg/day; (4) presence of diabetic retinopathy; and (5) negative serologic workup for other glomerular diseases, i.e., negative ANA, normal complement levels, negative hepatitis and HIV serologies, and no evidence of a paraprotein. At the time of screening, patients were instructed in a 0.8-g/kg/day protein, 4-g sodium, American Diabetes Association (ADA) diet. Patients were excluded if they had comorbid conditions that would preclude the use of the study medications, had a history of allergy to any of the medications, or if they were or wished to be pregnant.

Thirty-six patients were enrolled. Four patients were dropped within the first month because of noncompliance, and one patient in the captopril group developed acute renal failure with ultrasonographic evidence of obstructive uropathy at 4 months and was excluded from the analysis. Thus, 31 African Americans (14 men, 17 women) with a median age of 56 years (range, 27–70 yr) were studied; 16 patients were receiving insulin, 10 were treated with an ADA diet alone, and five with diet plus oral hypoglycemic agents. The majority of patients (29 of 31) were hypertensive and were treated with an average of two different antihypertensives (range, 1–4), including diuretics in 22 patients, CCB in 19, and CEI in 15. Of the 16 patients who were randomized to isradipine, seven were on CEI, and 12 were on CCB; in the 15 patients randomized to the captopril group, eight were on CEI, and seven were on CCB before baseline measurements. The latter two classes were discontinued at least 2 wk before baseline measurements. In the interim period, blood pressure was maintained at <160/90 with diuretics and/or clonidine. Two patients also required hydralazine for blood pressure control. Five patients were receiving a HMG-CoA reductase inhibitor, and this was continued.

**Baseline Assessment**

At baseline, patients submitted a 24-h urine specimen to measure creatinine clearance, total protein, urea nitrogen, and sodium. To measure GFR, five drops of a saturated solution of potassium iodide was given before the test. Diuresis was initiated with an oral water load of 10 ml/kg and maintained during the duration of the study by having each patient drink the same volume of urine voided. An intravenous cannula was inserted in the antecubital area for blood drawing, and, after baseline blood was obtained, 35 microCi of $^{125}$I-iothalamate were injected subcutaneously in the deltoid area of the contralateral arm. After an equilibration period of 60 min, four timed urine collections of 20–30 min duration were obtained, with blood drawn at the beginning and end of each collection period. GFR was calculated as the average of the four urinary clearances. Specific $^{125}$I activity was measured in duplicates of 1-ml blood and urine samples, using an Isodata 20/20 gamma counter (Palatine, IL).

Blood pressure was measured with a mercury sphygmomanometer in the standing position in the same arm at each visit. The systolic blood pressure was recorded at the appearance of phase I Korotkoff sounds, and the diastolic blood pressure at the disappearance of phase V Korotkoff sounds. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third the difference between systolic and diastolic pressures. Blood and urinary chemical analysis were performed in the hospital laboratory by standard techniques. Protein excretion was expressed as mg/mg urine creatinine to avoid inaccurate 24-h collections. Baseline values were obtained from one urine collection. Based on published observations, the coefficient of variation for proteinuria in diabetic patients is <10% (27, 28). HbA1C was measured by HPLC (normal values, 6.5%–8.0%). Dietary protein intake was calculated from the 24-h urea excretion, according to Maroni et al. (29).

**Randomization**

After baseline measurements were obtained, patients were stratified according to GFR and level of proteinuria (30), and randomized to receive either isradipine 2.5 mg orally twice daily or captopril 25 mg orally three times daily to achieve a standing blood pressure of <140/90 mm Hg. Management of diabetes was left to the care of their primary physicians.

Isradipine or captopril doses were increased up to 10 mg twice daily and 50 mg three times daily, respectively, on a weekly basis until the desired standing blood pressure was achieved. If needed, clonidine or beta-blockers were added. Diuretics were used at the discretion of the investigator for edema or blood pressure control. Patients were examined every 2 months to measure blood pressure and to perform routine blood tests, including hemoglobin A1C. Every 3 months, each patient submitted a 24-h urine specimen for creatinine clearance, total protein, urea nitrogen, and sodium. At 6 months, patients underwent GFR measurement as described above. The change in protein excretion was calculated as the ratio between the level of proteinuria at 6 months minus the level at baseline, divided by the baseline level of proteinuria.

**Statistical Analyses**

Results are expressed, unless indicated otherwise, as mean ± SE. Protein excretion levels were not normally distributed and, therefore, were log-transformed to approximate a normal distribution (31). Comparisons between the two treatment groups were made by unpaired t
test. Within each group, comparisons between baseline and 6 months results were made by paired *t* test. Serial longitudinal comparisons were made by ANOVA with repeated measurements. Results are considered significant if *P* < 0.05.

**Results**

Baseline clinical information is summarized in Table 1. For the 31 patients, GFR ranged from 24 to 145 ml/min/1.73 m², with an average of 62 ± 9 ml/min/1.73 m²; protein excretion ranged from 500 to 17,200 mg/day and averaged 3367 mg/day; serum creatinine was mildly elevated (average, 1.7 ± 0.2 mg/dl). Hypertension and obesity, as assessed from the body mass index (BMI), were present in most patients, and patients in the isradipine group had a higher BMI than in the captopril group (Table 1). There were no differences in age, gender, blood pressure, HbA1c, serum albumin, or cholesterol levels between the two groups (Tables 1 and 2). At randomization, GFR, protein excretion, and dietary protein and sodium intakes did not differ between the two groups (Table 2).

The longitudinal effects on renal function and protein excretion of the two classes of medications are shown in Table 3. At 6 months, MAP was similar in both groups (102 ± 3 versus 104 ± 3 mm Hg for isradipine and captopril, respectively), and GFR was preserved (Δ = −4 ± 3, isradipine; Δ = +1 ± 3 ml/min/1.73, captopril; *P* = NS). Proteinuria increased significantly by 60 ± 22% (*P* < 0.05) in the isradipine group. In contrast, captopril reduced proteinuria by 30 ± 15% (*P* < 0.05). The course of systemic blood pressure levels and protein excretion for the two groups is shown in Figure 1. The differential effect of isradipine and captopril on proteinuria was apparent after 3 months (Figure 1B) and reached statistical significance level at 6 months. A higher level of proteinuria was present in the isradipine group, despite a trend toward lower systemic blood pressure (as compared with the captopril group, Figure 1A). The differential effects on proteinuria of the two drugs were not related to changes in systemic arterial pressure (Figure 2). Neither MAP nor GFR significantly differed from baseline in either group at 6 months. There was no difference in protein or sodium intake between the two groups during the 6-month period. Serum albumin and cholesterol levels remained unchanged over the 6-month period in both groups (data not shown).

The two study medications were well tolerated. At 6 months, the mean isradipine dose was 16 ± 2 mg/day, and patients in this group were prescribed a total of 2.6 ± 0.2 antihypertensives, on average. Other antihypertensives included diuretics in 14, clonidine in seven, and beta-blockers in four. In the captopril group, the mean dose was 103 ± 15 mg/day, and patients were given 2.3 ± 0.3 medications, including captopril, on average. Three patients were receiving <75 mg/day of captopril because they had standing hypotension and were unable to tolerate the full dose. Eleven patients were also given diuretics; four, clonidine; and two, beta-blockers. No class-specific adverse reactions were encountered. Specifically, no patients receiving captopril developed hyperkalemia (although most of the patients were given loop diuretics), and serum creatinine remained stable in both groups.

**Discussion**

Despite having a higher prevalence of diabetes and being more prone to develop end-organ damage than Caucasians, African Americans have been underrepresented in most diabetic nephropathy studies. In hypertensive African Americans, CCB are more effective than CEI at lowering systemic blood pressure (19), which has been attributed to a "low-renin" state and to a higher sensitivity to the systemic vasodilatory effects of CCB (32). In non-African Americans with nephropathy, a growing body of evidence (33,34) suggests that CEI have a preferential antiproteinuric effect, as compared with other classes of antihypertensives, including CCB. To our knowledge, the study presented here is the first that addresses whether CCB and CEI affect proteinuria in diabetic African Americans in a similar way as in other ethnic groups. Our results support the concept that the two classes of antihypertensive drugs affect intraglomerular hemodynamics in African Americans and in Caucasians in the same fashion.

In the study presented here, we showed that isradipine significantly worsened proteinuria, on average by 50%, whereas captopril significantly reduced proteinuria by approximately 30%. In the isradipine group, the increase in proteinuria occurred, despite a trend toward lower systemic blood pressure during the study period as compared with baseline measurements (Figure 1A and 2), and it was not related to changes in GFR (Table 3). In the captopril group, the antiproteinuric effect occurred without changes in baseline systemic

**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Age* (yr)</th>
<th>Gender (M/F)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HbA1c (%)</th>
<th>Antihypertensive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isradipine (n = 16)</td>
<td>58 (26-67)</td>
<td>9/7</td>
<td>97 ± 5</td>
<td>34 ± 1</td>
<td>153 ± 7</td>
<td>83 ± 4</td>
<td>9.3 ± 0.6</td>
</tr>
<tr>
<td>Captopril (n = 15)</td>
<td>55 (27-71)</td>
<td>5/10</td>
<td>85 ± 3b</td>
<td>30 ± 1b</td>
<td>142 ± 5</td>
<td>86 ± 4</td>
<td>9.4 ± 0.7</td>
</tr>
</tbody>
</table>

*Note. Values are mean ± SE of patients in the two groups before receiving the medications. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin component.*

* Median values (range).

b *P* < 0.05 versus isradipine group.
Figure 1. Changes at 6 months from baseline in mean arterial pressure (x axis) and proteinuria (y axis) for the captopril (open circles) and isradipine groups (solid triangle). Mean ± SE, bar.

Figure 2. The levels of systolic and diastolic blood pressure over 6 months (upper panel, 1A), and changes in protein excretion as compared with baseline (lower panel, 1B). Captopril group, open circles or mottled bar; isradipine group, solid triangles or grey bar; *, P < 0.05 versus isradipine baseline; †, P < 0.05 versus captopril baseline.

blood pressure or GFR (Figure 2). Thus, the differential effects on proteinuria are not related to changes in systemic hemodynamics or GFR. We did not measure glomerular permselectivity in this study; however, it is reasonable to postulate that the changes in protein excretion reflect changes in glomerular permselectivity. This could be mediated either by an opposing direct effect of the two drugs on membrane porosity or, indirectly, by way of their differential ability to reduce intraglomerular pressure and modulate membrane pore size ("stretch-mediated"). In experimental models in rats, CCB dilate the afferent arteriole and have a minimal or no effect on efferent arteriolar tone (11,12); thus, the level of intraglomerular pressure will depend on the systemic blood pressure and the degree of afferent arteriolar vasodilation. In contrast, CEI dilate the efferent arteriole (35) and reduce intraglomerular pressure independently of the degree of systemic blood pressure reduc-

Table 2. Baseline clinical data

<table>
<thead>
<tr>
<th></th>
<th>Glomerular Filtration Rate (ml/min per 1.73 m²)</th>
<th>Serum Creatinine (mg/dl)</th>
<th>Serum Albumin (g/l)</th>
<th>Serum Cholesterol (mg/dl)</th>
<th>Proteinuria (mg/d)</th>
<th>Protein Intake (g/kg per day)</th>
<th>Urine Na (meq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isradipine</td>
<td>61 ± 9</td>
<td>1.9 ± 0.2</td>
<td>39 ± 2</td>
<td>255 ± 14</td>
<td>3023 ± 698</td>
<td>0.75 ± 0.09</td>
<td>167 ± 37</td>
</tr>
<tr>
<td>Captopril</td>
<td>63 ± 9</td>
<td>1.6 ± 0.2</td>
<td>38 ± 2</td>
<td>250 ± 11</td>
<td>3734 ± 1097</td>
<td>0.86 ± 0.07</td>
<td>144 ± 23</td>
</tr>
</tbody>
</table>

Table 3. Longitudinal renal function

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Mean Arterial Pressure (mm Hg)</th>
<th>Glomerular Filtration Rate (ml/min per 1.73 m²)</th>
<th>Proteinuria (mg/mg creatinine)</th>
<th>Dietary Protein Intake (g/kg per day)</th>
<th>Urine Na (meq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>106 ± 4 102 ± 3</td>
<td>61 ± 9</td>
<td>58 ± 9</td>
<td>2.01 ± 0.40</td>
<td>0.75 ± 0.09</td>
</tr>
<tr>
<td>6</td>
<td>102 ± 3 102 ± 3</td>
<td>64 ± 11</td>
<td>64 ± 11</td>
<td>2.30 ± 0.70</td>
<td>0.83 ± 0.04</td>
</tr>
</tbody>
</table>

* P < 0.05 versus respective baseline values.
formation. However, CEI also have a membrane pore size-modulating effect (36). Thus, the mechanism(s) of the differential effect on protein excretion in patients cannot be ascertained from this study. However, it is worth noting that in a uninephrectomized diabetic rat model, Anderson et al. (7) found that the CCB, nifedipine, although effective at reducing systemic blood pressure, did not reduce proteinuria or prevent histologic damage, as compared with the CEI, fosinopril. This was associated with a persistence of high glomerular capillary hydraulic pressures in the nifedipine-treated group.

In experimental models of deoxycorticosterone-salt hypertension, CCB protect against glomerular sclerosis by modulating glomerular hypertrophy without normalizing intraglomerular pressure (8). This has not been confirmed in diabetic rat models (7,10). In dogs with alloxan-induced diabetes, a diltiazem-like CCB has been shown to reduce proteinuria and to protect against mesangial expansion and segmental sclerosis (16). Although intraglomerular pressure was not measured in that study, it is postulated that the renal protective action of the diltiazem-type blocker results from the ability of this particular class of CCB to reduce efferent arteriolar tone and, thus, to normalize glomerular capillary pressure.

Are these changes in proteinuria clinically important? Despite differences in protein excretion, GFR was preserved in both groups at 6 months, and there were no changes in serum albumin, cholesterol, or the dose of lipid-lowering drugs in either group at 6 months compared with baseline. However, in diabetic nephropathy, progression of renal disease is measured in years rather than months, so identification of isradipine-induced worsening of proteinuria and changes in the course of diabetic nephropathy could require longer follow-up. In experimental models with diabetes, amelioration of injury is always accompanied by improvement in proteinuria, and in humans, the degree of proteinuria correlates with the rate of progression in both diabetic (37) and nondiabetic (38) glomerular diseases. The reason for this association is not known, but excessive proteinuria is likely to be a consequence of a more severe injury to the glomerular capillary wall. In support of this, we and others have found a negative correlation between the prominence of the shunt pathway and the total numbers of glomerular membrane restrictive pores, as assessed by the dextran sieving technique, in glomerulopathic patients (31,39). Thus, as proteinuria worsens, the glomerular ultrafiltration capacity decreases. Moreover, the increased transglomerular trafficking of proteins could have other deleterious effects by promoting glomerular sclerosis (40). Proteinuria could also contribute to progressive injury by direct toxic effect on the tubules, by inducing tubular cell expression of inflammatory (41) and vasoactive molecules (42), and by potentiating interstitial fibrosis (43). Irrespective of the mechanism(s), a reduction in proteinuria in patients with diabetes correlates with a more benign course (44).

In summary, our results show that the angiotensin CEI, captopril, reduces proteinuria in African Americans with diabetic nephropathy, suggesting that CEI may have a therapeutic role in these patients. In contrast, the CCB, isradipine, worsens proteinuria, and this class of drugs may have deleterious effects in African Americans with diabetic nephropathy.

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References