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Beta-blockers have a Beneficial Effect upon Endothelial Function and Microalbuminuria in African-American Subjects with Diabetes and Hypertension

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Abstract

Background—Type-2 Diabetes Mellitus(T2DM) with microalbuminuria(MA) is associated with increased risk of cardiovascular events(CVE) that may be attenuated by Angiotensin-Converting-Enzyme Inhibitors(ACEIs), unless microalbuminuria persists(PMA). African-Americans(AA) have a higher prevalence of nephropathy with suboptimal response to ACEIs. We studied the effects of beta-blockers addition and comparative effects of carvedilol with metoprolol on 24-hour urinary-albumin excretion(UAE) and endothelial function(EF) in AA with PMA.

Methods—Thirty-four AA 30–70 years age with T2DM and PMA despite ACEI therapy were randomized to receive carvedilol or metoprolol in addition to ACEI and any other concurrent therapy. Carvedilol/metoprolol dose was titrated to achieve blood pressure(BP)<130/80mmHg. UAE and brachial-artery reactivity were studied at baseline and 12-weeks. We analyzed the effects of addition of beta-blockers and whether there was any difference in response between the two beta-blockers.

Results—Thirty-three subjects completed the study; BP decreased to <135/80mmHg. After 12-weeks, beta-blocker treatment resulted in significant increase in flow-mediated dilatation(FMD) from $3.5 \pm 1\%$ to $8.5 \pm 1\%$ ($p=0.004$) and significant reduction in mean log-transformed UAE from $2.655 \text{ gm/gm Cr} \pm 0.087$ to $2.533 \text{ gm/gm Cr} \pm 0.093$ ($p=0.028$). FMD increased by 240% ($p=0.033$) with carvedilol and by 110% ($p=0.096$;NS) with metoprolol. UAE decreased with carvedilol by 0.35 gm/gm Cr ($p=0.023$) and with metoprolol by 0.23 gm/gm Cr ($p=0.298$;NS).

Conclusion—Our results clearly indicate that addition of beta-blockers to ACEI improves EF and reduces UAE in high risk AA T2DM patients with PMA. Carvedilol but not metoprolol improves EF and reduces UAE in AA with identical BP control. Larger trials are needed to further elucidate the differential effects of carvedilol/metoprolol on EF and UAE and its impact on CVE in such patients.

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Keywords

Type 2 Diabetes Mellitus; Beta-Blockers; African American; Endothelial Function; Microalbuminuria

Introduction

Patients with diabetes mellitus are more susceptible to the vascular complications of hypertension (1). This risk is greatly increased when patients develop microalbuminuria and proteinuria. African American subjects have high prevalence of nephropathy (2), with clinically significant proteinuria being reported as high as in 36% of persons at the time of diabetes diagnosis (3). African Americans develop nephropathy earlier than Non-Hispanic whites after short duration of diabetes (4).

The risk of cardiovascular events and renal disease progression may be attenuated by treatment with angiotensin converting enzyme inhibitors (ACE inhibitors), and such treatment has now become standard practice in the management of such patients. Nevertheless, several clinical problems remain. The progression of nephropathy is not completely halted in patients treated with ACE inhibitors. Proteinuria is decreased but still remains present in a large percentage of patients. Finally, data suggest that some patients, particularly African Americans, do not respond adequately to ACE inhibitors and therefore continue to have uncontrolled hypertension and proteinuria (5;6).

Following the development of microalbuminuria and proteinuria, patients with diabetes have a considerable increased risk of cardiovascular disease. The reasons for the increased risk are unclear but may be related to several abnormalities, the most prominent of which appears to be endothelial dysfunction (7). ACE inhibitors have been shown to have a beneficial effect on improving vascular reactivity (8). However, we have recently demonstrated that in African American patients with proteinuria that persists despite optimal ACE inhibitor therapy, endothelial function is severely impaired compared to both matched patients whose proteinuria resolved as well as similarly affected Non-Hispanic whites (9).

A previous study has demonstrated the value of the addition of beta-blockers to patients treated with blockade of the rennin – angiotensin system in achieving BP goals in patients with diabetes (10). In addition, the study showed a benefit of carvedilol over metoprolol in terms of reducing microalbuminuria. Carvedilol is an anti-hypertensive drug with non-selective beta-adreno-receptor and selective alpha-adreno-receptor blocking activity. In addition, carvedilol prevents lipid peroxidation and the depletion of endogenous anti-oxidants. (11). Furthermore carvedilol has also been shown to have a potential for improving endothelial function by decreasing ET-1 production as well as its anti-oxidant effect (12). However, these effects have not been tested in the setting of optimal ACE inhibitor treatment in high risk patients.

In view of the above potential for improving known abnormal parameters in high-risk patients, we studied the effects of carvedilol in comparison with the effects of metoprolol. Our hypothesis was that beta –blocker treatment would improve endothelial function and decrease albumin excretion. We further wished to test the hypothesis that carvedilol would be superior to metoprolol when used in combination with an ACE inhibitor in decreasing albumin excretion and improving endothelial function in such patients.

Methods

The study was approved by Tulane Human Research Advisor Committee (IRB). Subjects included 34 patients enrolled through diabetes clinics at Tulane University Medical Center and Charity Hospital. All participants provided informed consent before they were entered into the study. Subjects were between the ages of 30 and 70 with type 2 diabetes mellitus (typical history to suggest type 2 and negative for antibodies to glutamic acid decarboxylase) and known microalbuminuria (above 30 mg albumin/g creatinine) or overt proteinuria (above 300 mg albumin/g protein) already being treated with an ACE inhibitor. Patients with congestive heart failure, asthma, known hypersensitivity reactions to a beta-blockers, pregnancy or serum creatinine greater than 2.0 were excluded from the study. All patients continued their baseline medications throughout the study. Their baseline characteristics are summarized in Table 1.

At enrollment, all subjects underwent 24-hour urine collection for albumin excretion rate measurement. Urinary creatinine was also measured to assure adequate urine collection. In addition, blood pressure was measured and brachial artery reactivity study to assess endothelial function was performed. Patients were then randomized to receive, in a double-blind manner, either carvedilol (N=18) or metoprolol (N=16), added on to their usual ACE inhibitor therapy. Both metoprolol and carvedilol were dispensed to the subjects by the randomizing pharmacist in identical appearing capsules. At each follow up visit, subjects were asked to bring medication bottles with them. Subjects were interviewed about compliance with medication and remaining medication capsules were counted for confirmation. In this study, >95% medication compliance was achieved.

Patients randomized to carvedilol were started with 6.25 mg twice a day (Dose Level 1) for one week. If blood pressure did not reduce to target (<130/80 mm Hg), the dose was increased to 12.5 mg twice a day (Dose Level 2) for one week. If the patient did not respond with a further blood pressure decrease to target level, the dose was increased to 25 mg twice a day (Dose Level 3), the highest dose of study medication.

Patients randomized to metoprolol were started with 50 mg twice a day (Dose Level 1) for one week. If blood pressure was not reduced to target (<130/80 mm Hg), the dose was increased to 100 mg twice a day (Dose Level 2) for one week. If the patient did not respond with a further blood pressure decrease to target level, the dose was increased to 200 mg twice a day (Dose Level 3), the highest dose of study medication.

Following 12 weeks of study treatment, blood pressure determination, brachial artery reactivity study to assess endothelial function and 24-hour urine collection for albumin excretion rate were repeated.

Endothelial function

Endothelial function was assessed by measuring brachial artery reactivity on ultrasound. Two-dimensional images from a 7.5 MHz ultrasound transducer were used to determine the diameter of the brachial artery and the velocity of blood flow was determined by Acuson XP120 Ultrasonograph. The subject rested in the supine position for at least five minutes. A continuous electrocardiogram (EKG) tracing was recorded. A baseline scan for the diameter of the brachial artery was recorded at a point 2–10 cm above the antecubital fossa. Baseline arterial flow velocity was measured with a pulsed Doppler signal at an angle of 70°, with the range gate (1.5 mm) in the center of the artery. Increased flow will then be induced by inflating a pneumatic tourniquet placed over the arm to a pressure 40-mm Hg above the systolic pressure for at least 5 minutes and then deflating the cuff. The scan was recorded for 90 seconds after cuff deflation. The flow velocity and the flow-mediated change in the vascular diameter were recorded at 60 seconds after cuff deflation. The scans were recorded on a videotape for later analysis. Vessel

diameter was measured by 2 independent observers as an average of readings taken during 4 cardiac cycles at end diastole, incident with the R-wave on the continuous EKG tracing. Flow was calculated from the Doppler flow velocity and the vessel diameter. After 15 minutes rest another scan was performed to assure the return to arterial baseline diameter. Sublingual nitroglycerin 400 microgram was then administered and the final scan was performed 3 minutes later. Vessel diameters of reactive hyperemia, 15 minutes rest, and 3 minute post nitroglycerin administration were expressed as percentages of the first control scan.

Albumin Excretion

Subjects were asked to collect 24-hour urine for protein and creatinine excretion at baseline and at 12-week visit. Subjects were provided with instructions about proper collection, storage and transportation of urine specimen. Appropriate containers were provided to subjects before each respective visit. Each container was appropriately labeled and sent to core GCRC laboratory for analysis.

Statistical Analysis

SPSS software version 14.0 was used to conduct statistical analysis. Continuous variables were compared using ANOVA. Urine albumin excretion in our patients was not normally distributed and had a considerably large variability. We therefore log transformed the data for further statistical analysis. Baseline and 12 week log transformed data in each treatment group was compared using paired t-test. An alpha level of 0.05 was considered to be significant.

Results

Our initial intent was to randomize 40 patients in this study. However, due to a natural disaster (hurricane Katrina) we had to close the trial after 34 patients were randomized in the study. Of these, 33/34 subjects completed the study. One subject (randomized to carvedilol treatment group) was unable to follow up after the baseline visit due to personal reasons. None of the subjects enrolled had any serious adverse reaction during the study period.

The results of blood pressure measurements, brachial artery reactivity study and 24-hour urine for albumin excretion are shown in Table 2. Statistically significant reductions in both systolic and diastolic blood pressures were observed in both treatment groups, and the average blood pressure at the end of the study was less than 135/80 mmHg. There was no difference in blood pressure between groups at the end of the study. The mean dose of carvedilol and metoprolol required by subjects at the end of study was 36.5 mg/day and 138.5 mg/day respectively, administered twice daily. There was considerable variability in the 24 hour urinary excretion rates which were not normally distributed. Therefore this data was log transformed before analysis.

The combined metoprolol and carvedilol study subject data at baseline was compared with after twelve weeks of treatment with either of the beta-blockers. After 12 week treatment, beta-blocker treatment resulted in a statistically significant increase in FMD from $3.5 \pm 1\%$ to $8.5 \pm 1\%$ ($p=0.004$) whereas the NDD did not increase significantly (10 ± 1 vs. $9\pm 1\%$; $p=0.279$) (Figure 1). After 12 weeks, beta-blocker treatment resulted in a statistically significant reduction in mean log transformed 24-hour UAE from $2.655 \text{ gm/gm Cr} \pm 0.087$ to $2.533 \text{ gm/gm Cr} \pm 0.093$ ($p=0.028$) (Figure 2).

The mean brachial artery flow-mediated dilation increased 5.5%, a 240% increase ($p = 0.033$) with carvedilol, whereas there was a non-significant increase in the metoprolol group of 5.2%, a 100% increase from baseline ($p = 0.096$). The mean log transformed 24-hour UAE with

carvedilol fell by 0.35 gm/gm Cr ($p = 0.023$), and with metoprolol by 0.23 gm/gm Cr ($p = 0.298$).

Discussion

Our data demonstrate that in African American subjects with persistent microalbuminuria treated with ACE inhibitors, it is possible to decrease blood pressure further by addition and titration of a beta-blocker. Beta-blockers as a class effect reduce microalbuminuria and improve endothelial function in African American type 2 diabetic patients. Furthermore, carvedilol reduced urinary albumin excretion and improved endothelial function in this population. Due to the high risk of cardiovascular events and mortality in such patients (13;14) these findings may have clinical implications for choice of therapy in such high risk patients. These findings add to and extend those of the GEMINI study(10), with particular importance to a population at very high risk of disease progression and mortality. The difference between the carvedilol and metoprolol treated groups in terms of endothelial function improvement was modest but still statistically significant. However, larger trials with greater statistical power may be needed to further elucidate the differential effects of carvedilol and metoprolol on endothelial function and microalbuminuria.

African Americans have a higher prevalence of hypertension and suffer an increased burden of its sequelae compared to Non-Hispanic Whites. In one study, out of 932 African American adults sampled, only 27% of those with hypertension would be classified as controlled if both the 140 mmHg systolic and the 90 mmHg diastolic criteria were applied. Seventy-five percent of the study subjects would be controlled if only the 90 mmHg diastolic criterion were used (15).

There is no consensus on the optimal treatment of such patients. African Americans are relatively resistant to the antihypertensive effects of ACE inhibitors but respond well to calcium channel blockers (CCB). However, in contrast to their effects on hypertension in one study, captopril, an ACE inhibitor, reduced and isradipine, a CCB, increased proteinuria in African Americans with type 2 diabetes mellitus and nephropathy (16). Beta-blockers in general have been felt to be less than perfect choice for hypertension control in African Americans (17–19). Thus, a variety of reasons have led to under prescription of beta-blockers in African American population including a perception of their being less efficacious in slowing the rate of glomerular filtration rate decline in subjects with mild to moderate hypertensive renal insufficiency (18;19) and considerably less blood pressure reduction in during monotherapy with nonselective beta-blockers than with diuretics (17). Our study clearly demonstrates that beta-blockers are not only safe and effective choice of hypertensive but also have a beneficial effect on endothelial function and nephropathy in high risk type 2 diabetic African Americans.

ACE inhibitors may provide an added degree of protection to the diabetic kidney, independent of their arterial pressure-reducing effects (20). This observation, however, is derived largely from studies in Non-Hispanic Whites, and questions have been raised about the applicability of such therapy in other ethnic groups.(21) The issue of race-based choice of therapy is controversial (22). Nevertheless, a combination of fixed dose of both isosorbide dinitrate and hydralazine has been approved by the FDA specifically for African Americans with heart failure, the decision being based on a large clinical trial (22;23). It is noteworthy that the rationale for that study was that African American patients have particular problems with nitric oxide production. Indeed, in our previous study (9) we have demonstrated that FMD is lower in African American patients and we have demonstrated a severe abnormality in endothelial function in our patients.

It is noteworthy that we achieved an average blood pressure less than 135/80 mmHg in both treatment groups, compatible with the data from the GEMINI trial (10) and once again demonstrating that beta-blockers are effective in combination with ACE inhibitors in treating hypertension associated with diabetes. Recent data suggests that African Americans with nephropathy require arterial pressure reductions significantly below that of whites to produce a comparable preservation of renal function even with the use of ACE inhibitors (24;25). Since participants in both treatment groups of our study were African Americans and the blood pressure control was identical, a potential confounding variable due to different blood pressure lowering was removed.

Previous studies have demonstrated that African Americans respond differently to different antihypertensives in regards to reduction in proteinuria and rate of decline in creatinine clearance. In a study by Bakris et al, after a mean follow-up of 54±6 months, the calcium channel blocker group demonstrated both a slower rate of decline in creatinine clearance (-1.7 ± 0.9 versus -3.7 ± 1.4 mL/min per year per 1.73 m^2 , $P < 0.01$) and a greater reduction in proteinuria compared with the atenolol group. Additionally, a greater proportion of the atenolol group had a 50% or more increase in serum creatinine compared with the verapamil group ($32 \pm 9\%$ versus $16 \pm 7\%$, $P < 0.05$). These differences could not be explained by differences in blood pressure control (26). The reasons for the lack of response to ACE inhibitors in some patients are not clear and may be genetically determined. However, we have not examined this issue in our study and further research is needed to optimally target therapy. Both groups in our study decreased albumin excretion and improved brachial artery flow-mediated dilatation. Perhaps some of this improvement could be attributed to the reduction in blood pressure. However, the reduction in albumin excretion only reached statistical significance with carvedilol, perhaps reflecting a more consistent reduction in most of the patients, whereas it was variable with metoprolol. Similarly, the increase in flow-mediated dilatation with carvedilol was more consistent and to a greater degree relative to baseline, resulting in statistical significance. Both groups were well matched at baseline in terms of protein excretion and blood pressure. However, the flow-mediated dilatation at baseline was much lower in the group randomized to carvedilol. The flow-mediated dilatation in these patients was severely impaired despite ACE inhibitors, a treatment known to improve flow-mediated dilatation (27). The nitroglycerine responsiveness in our patient did not change with treatment in either group, suggesting that the improvements seen are likely to be due to improvement in nitric oxide production rather than nitric oxide action.

We conclude that in African American patients with persistent microalbuminuria despite ACE inhibitor therapy, adding beta blockers to their antihypertensive therapy leads to significant improvement in blood pressure, endothelial function and albumin excretion rates. Furthermore, on analysis of the individual beta blockers our data suggests that treatment with carvedilol, but not metoprolol, leads to significant improvement in endothelial function and reductions in urinary protein excretion. These findings may have implications for the prevention of cardiovascular disease in this high risk population.

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Figure 1.
Effects of 12 Weeks Treatment with Beta Blockers in Flow Mediated Dilatation (FMD) and Nitroglycerine Dependent Dilatation (NDD)

Figure 2.
Effect of 12 Weeks Treatment with Beta Blockers on Log Transformed 24 Hour Urinary Excretion rate (UAE)

Table 1

Baseline Characteristics Of Subjects Randomized To Carvedilol Or Metoprolol Treatment. None Of The Baseline Characteristics Were Different Between Groups.

	CARVEDILOL	METOPROLOL	<i>p</i> -value (carvedilol vs. metoprolol group)
Number	18	16	-
Age (range)	52.5 (33–70)	53.5 (30–70)	-
Sex M : F	5 : 13	7 : 9	-
Mean Log Baseline Proteinuria/Gram Creatinine $\pm$SD	6.15 $\pm$ 1.15	6.13 $\pm$ 1.18	0.9
BMI $\pm$SEM	33.44 $\pm$ 2.6	31.6 $\pm$ 3.6	0.5
A1C $\pm$SEM	10.2 $\pm$ 0.5	8.8 $\pm$ 0.5	1.0
GFR : (MDRD method)ml/min/1.73 m² $\pm$SEM	94 $\pm$ 9.6	78 $\pm$ 8.1	0.3
GFR: (Cockcroft-Gault)ml/min/1.73 m² $\pm$SEM	129 $\pm$ 18	102 $\pm$ 24	0.4
Serum Creatinine	1.033 $\pm$ 0.12	1.15 $\pm$ 1.0	0.5
Total Cholesterol	179 $\pm$ 12.8	189 $\pm$ 10	0.5
LDL Cholesterol	103 $\pm$ 11.6	116 $\pm$ 8	0.3
HDL Cholesterol	40 $\pm$ 2.6	44 $\pm$ 4.2	0.43

Table 2

Effect Of Carvedilol And Metoprolol On Blood Pressure, Urinary Albumin Excretion Rate And Endothelial Function In African-American Patients With Proteinuria Despite ACE Inhibition. All Values Are Reported As Mean $\pm$ SD Unless Stated Otherwise

	CARVEDILOL	p-value (Baseline vs. 12-weeks)	METOPROLOL	p-value (Baseline vs. 12-weeks)	p-value (carvedilol vs. metoprolol)
Mean Log 12-Week Proteinuria/Gram Creatinine	5.8 $\pm$ 1.2	0.023	5.9 $\pm$ 1.2	0.298	0.8
Mean Baseline Systolic Blood Pressure (mmHg) $\pm$ SEM	146 $\pm$ 6	-	147 $\pm$ 7	-	0.95
Mean 12-Week Systolic Blood Pressure (mmHg) $\pm$ SEM	134 $\pm$ 4	0.047	131 $\pm$ 4	0.046	0.63
Mean Baseline Diastolic Blood Pressure (mmHg) $\pm$ SEM	86 $\pm$ 3	-	84 $\pm$ 4	-	0.51
Mean 12-Week Diastolic Blood Pressure (mmHg) $\pm$ SEM	78 $\pm$ 3	0.016	76 $\pm$ 3	0.027	0.55
Mean Baseline Flow mediated dilatation	2.3%	-	4.6%	-	0.641
Mean 12-Week Flow mediated dilatation	7.8%	0.033	9.8%	0.096	0.308
Mean percent Increase in FMD	240%	-	110%	-	-
Mean Baseline Nitroglycerine-Dependent dilatation	10%	-	11%	-	0.65
Mean 12-Week Nitroglycerine-Dependent dilatation	10%	0.655	12%	0.519	0.22