Reduction of microalbuminuria in type-2 diabetes mellitus with angiotensin-converting enzyme inhibitor alone and with cilnidipine

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ABSTRACT

The aim of our study was to find out the antiproteinuric effect of enalapril angiotensin-converting enzyme (ACE inhibitor) alone or in combination with cilnidipine in patients with type-2 diabetes mellitus. The study was conducted on 71 patients with type-2 diabetes mellitus patients with hypertension and microalbuminuria. They were divided into two groups randomly as follows: Group I (enalaprilalone, *n* = 36) and Group II (enalapril with cilnidipine, *n* = 35). In both the groups, baseline 24 h urinary albumin was estimated and was repeated every 3 months upto 1-year. After 1-year follow-up, reduction in microalbuminuria was found to be greater in Group II. In Group I microalbuminuria came down by 25.68 ± 21.40 while in Group II it reduced by 54.88 ± 13.84 ($P < 0.001$). We conclude that in diabetic population, cilnidipine has an additive effect in microalbuminuria reduction over and above the well-proven effect of ACE inhibitors.

Key words: Angiotensin-converting enzyme inhibitors, diabetic nephropathy, microalbuminuria

Introduction

Diabetic nephropathy is characterized by the onset of microalbuminuria, which progresses to overt proteinuria. Reduction of microalbuminuria leads to reduced risk of adverse renal and cardiovascular events.[1-4] Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blocker (ARBs) have been established to be first-line drugs in preventing the development and retarding the progress of diabetic nephropathy by reducing microalbuminuria.

Other drugs are effective in reducing proteinuria in diabetic nephropathy. Among these, cilnidipine, a unique dihydropyridine derivative 4th generation Ca^{2+} channel blocker has a rational pharmacological profile of dual L/N-type Ca^{2+} channel blocking action. It blocks L-type calcium channels in vascular smooth muscle and N-type calcium channels in sympathetic nerve terminals that supply blood vessels. In diabetic patients, there is enhanced sympathetic nervous activity resulting in constricted efferent arterioles and elevated intraglomerular pressure.[5] Unlike L-type calcium channel blockers, which cause only afferent arteriolar dilatation and increase in the intraglomerular pressure, this drug dilates both afferent and efferent arterioles by its effect on N-type calcium channels and thusreduces urinary albumin and protein excretion to a greater extent.[5-7]

As ACE inhibitors and cilnidipine has different mechanism of action in reducing microalbuminuria, both may be combined to get the added benefit of the two classes of drugs.

The aim of study was to compare the reduction in microalbuminuria in diabetic patients with hypertension by dividing them into two groups and keeping them under two different regimens. Group I was given enalapril (ACE inhibitor) alone and Group II was kept on combination therapy of enalapril and cilnidipine.

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Materials and Methods

Study population

The present study was a randomized prospective studyin type-2 diabetic patients attending diabetic OPD, medical OPD and admitted in indoor medical wards of King George's Medical University, Lucknow over a period of 1-year (August 2013 to July 2014). Ethical clearance from the institutional ethics committee was obtained. Informed consent was obtained from all the patients before the start of study.

The patients included in the study were subjects with type 2 diabetes mellitus (age 21–70 years, either gender) with hypertension and microalbuminuria (if two out of three 24 h urinary albumin measurements are in the range of 30–300 mg/24 h during an 8-week period before entry) and have had effective glomerular filtration rate (eGFR) >60 ml/min. Microalbuminuria was measured by chemiluminescent immunoassay.

The patients with type-1 diabetes mellitus, macroalbuminuria, normal blood pressure (BP), chronic kidney disease withe GFR<60 ml/min, chronic liver disease, coronary artery disease, urinary tract infection, and pregnant and lactating women were excluded from the study. Patients were excluded could not stay on medications and were not regular on follow up.

Total number of patients screened for microalbumiuria was 260. Out of these patients, 95 normoalbuminurc and 72 with overt proteinuria were excluded from the study. Out of these excluded patients, 54 patients were normotensive. Remaining 93 patients with type-2 diabetes mellitus were microalbuminuric and hypertensive. They were randomly allocated in the two groups: Group I-enalapril (n = 48) and Group II-enalapril with cilnidipine (n = 45). The baseline characteristics of the patients in the two groups are mentioned in Table 1. On comparison of characteristics in both the studied groups, the result was nonsignificant [Table 1 and Figure 1].

Table 1: Comparison of baseline characteristics of the two groups

Variable	Mean±SD		*P*
	Group I (*n*=36)	Group II (*n*=35)	
Age	54.06±9.46	52.89±9.11	NS
Sex (male/female)	20/16	20/15	NS
BMI (kg/m^2)	26.8±4.1	27.2±3.8	NS
SBP (mm Hg)	150.06±6.15	149.20±5.89	NS
DBP (mm Hg)	86.83±6.68	86.69±6.32	NS
Hb (g/dl)	11.47±1.94	10.84±1.72	NS
HbA1c (%)	7.38±0.63	7.51±0.85	NS
FBS (mg/dl)	187.22±59.96	185.03±50.78	NS
PPBS (mg/dl)	258.31±69.59	260.51±71.66	NS
Serum Na (meq/l)	137.11±4.18	136.37±4.25	NS
Serum K (meq/l)	4.12±0.52	4.25±0.48	NS
Serum urea (mg/dl)	36.72±7.33	36.27±7.82	NS
Serum creatinine (mg/dl)	0.92±0.19	0.96±0.25	NS
eGFR (ml/min/1.73 m^2)	78.72±20.18	77.37±22.67	NS
TC (mg/dl)	155.08±51.25	139.29±48.08	NS
TG (mg/dl)	157.50±67.21	170.83±74.05	NS
HDL (mg/dl)	45.44±12.81	42.09±14.41	NS
LDL (mg/dl)	80.67±35.94	74.14±22.09	NS
VLDL (mg/dl)	35.11±10.36	36.31±10.24	NS

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HbA1c: Glycosylated hemoglobin, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, Na: Sodium, K: Potassium, eGFR: Effective glomerular filtration rate, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, NS: Nonsignificant, SD: Standard deviation. As shown in the table, on comparison of patient's characteristics in both the studied groups, the result was NS

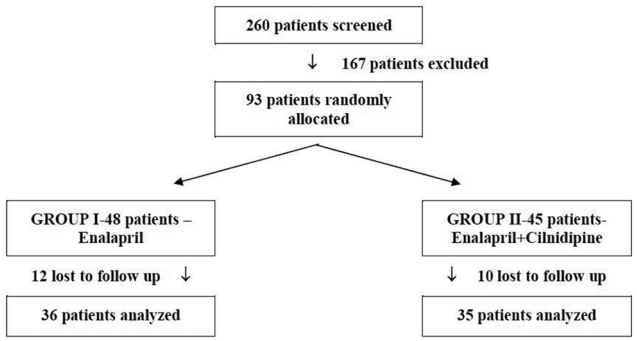

Figure 1: Flow chart of participants through the trial

Intervention

The patients in Group I received enalapril once a day at 2.5–10 mg/day to keep the BP under 140/90. Amlodipine was needed in five patients in addition to enalaprilin Group 1 to maintain BP<140/90. In Group II, the patients were given enalapril 2.5–10 mg/day and cilnidipine 10–20 mg/day to achieve a BP below 140/90.

After the start of this trial, 12 patients withdrew from Group I and 10 patients from Group II during the course of study. The chief reason for withdrawal was noncompliance. So the total number of patients who actually went through the study was 36 in Group I and 35 in Group II. 24 h urinary albumin was repeated every 3 months upto 1-year in both the groups. At the end of 1-year, the reduction in microalbuminuria was compared in both groups. During the course of the trial, patients were observed for any adverse outcome.

Statistical analysis

The results were presented as mean ± standard deviation (SD) and percentage. Chi-square test was used to compare the dichotomous/categorical variables. The unpaired t-test was used to compare two means. One-way analysis of variance was used to detect significant differences in the mean values. $P < 0.05$ was considered significant. All the analysis was carried out using Statistical Package for Social Sciences version 16 (Chicago, Inc., USA).

Results

The mean 24 h urinary albumin level in Group I at the start of study was 204.69 ± 50.34 mg and in Group II was 206.74 ± 50.95 mg. At the end of 12 months, the mean microalbuminuria level was 153.17 ± 54.10 mg in Group I and 93.51 ± 36.30 mg in Group II ($P < 0.001$). The mean percentage reduction from baseline at the end of 12 months in Group I was −25.68 ± 21.40% while in Group II it was −54.88 ± 13.84%, ($P < 0.001$) [Figures 2 and 3].

There was a significant reduction in systolic and diastolic B Pin both the groups from baseline to 1 year, but the difference in change of BP between Group I and Group II at different intervals was not significant. In Group I, one patient progressed to overt proteinuria while in Group II nobody progressed from microalbuminuria to overt proteinuria, although the difference was not significant. Again in Group I, only one patient became normoalbuminuric during the course of study while in Group II, it happened with three patients, although the difference was not significant. The correlation between percentage change in BP and percentage change in microalbuminuria was of random nature ($P > 0.05$) and showed a virtually nonexistent negligible relationship ($r > 0.3$) in random directions at different time intervals.

On comparison at baseline and throughout the follow-up periods, no significant difference was observed in mean systolic blood pressure levels of the two groups [Table 2].

At baseline and throughout the follow-up periods, no significant difference was observed in mean diastolic blood pressure levels of the two groups [Table 3].

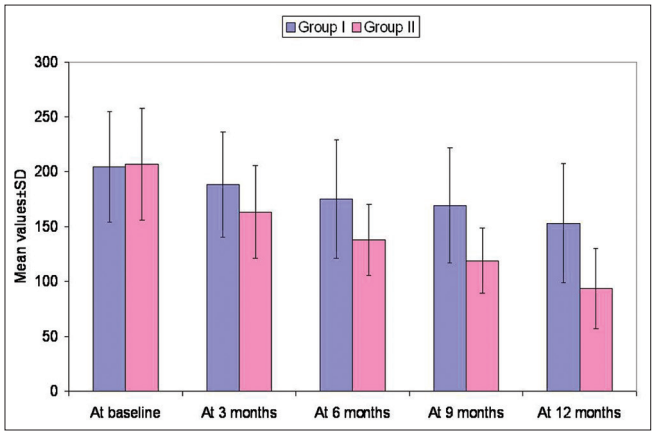

Figure 2: Comparison of microalbuminuria between two groups at baseline and different follow-up intervals. Results are expressed as mean ± standard deviation. After 1-year, the level of microalbumin in Group 1 was 153.17 mm Hg while in Group 2, it was 93.51 mm Hg ($P < 0.001$)

There were no adverse cardiovascular events in either group [Table 4]. There were no significant changes in serum creatinine, HbA1c and serum potassium levels

Table 2: Comparison of SBP between two groups at baseline and different follow-up intervals

Parameter (mg/dl)	Mean±SD		Statistical significance	
	Group I (*n*=36)	Group II (*n*=35)	*t*	*P*
At baseline	150.06±6.15	149.20±5.89	0.599	0.551
At 1-month	140.06±5.18	138.23±5.57	1.434	0.162
At 2 months	131.78±5.28	129.74±5.66	0.797	0.428
At 3 months	132.83±4.64	131.34±5.01	1.301	0.204
At 4 months	129.33±5.66	128.91±5.25	0.323	0.748
At 5 months	129.06±3.42	130.20±3.76	1.337	0.192
At 6 months	130.78±5.16	130.00±5.20	0.633	0.529
At 7 months	129.56±5.95	129.14±5.83	0.295	0.769
At 8 months	128.94±5.98	130.06±6.13	0.779	0.442
At 9 months	133.83±4.84	132.46±5.02	1.171	0.251
At 10 months	129.06±5.18	128.63±5.35	0.342	0.734
At 11 months	128.67±6.61	128.40±6.72	0.169	0.867
At 12 months	129.17±5.50	128.11±5.25	0.830	0.413

SBP: Systolic blood pressure, SD: Standard deviation

Table 3: Comparison of DBP between two groups at baseline and different follow-up intervals

Parameter (mg/dl)	Mean±SD		Statistical significance	
	Group I (*n*=36)	Group II (*n*=35)	*t*	*P*
At baseline	86.83±6.68	86.69±6.32	0.096	0.924
At 1 month	83.39±4.32	82.00±4.39	1.343	0.184
At 2 months	82.61±4.92	81.29±5.02	1.119	0.272
At 3 months	81.94±4.57	81.83±4.51	0.107	0.915
At 4 months	81.56±3.68	80.66±3.68	1.030	0.311
At 5 months	81.83±3.98	81.89±4.11	–0.055	0.957
At 6 months	81.56±3.18	81.54±3.33	0.016	0.987
At 7 months	80.56±4.96	81.51±5.07	0.798	0.431
At 8 months	80.56±4.40	80.69±4.44	0.124	0.902
At 9 months	81.22±4.81	81.31±4.80	–0.081	0.936
At 10 months	79.67±5.75	79.60±5.74	0.049	0.961
At 11 months	80.64±3.77	80.57±3.71	0.076	0.940
At 12 months	80.06±3.59	79.23±3.84	0.941	0.354

DBP: Diastolic blood pressure, SD: Standard deviation

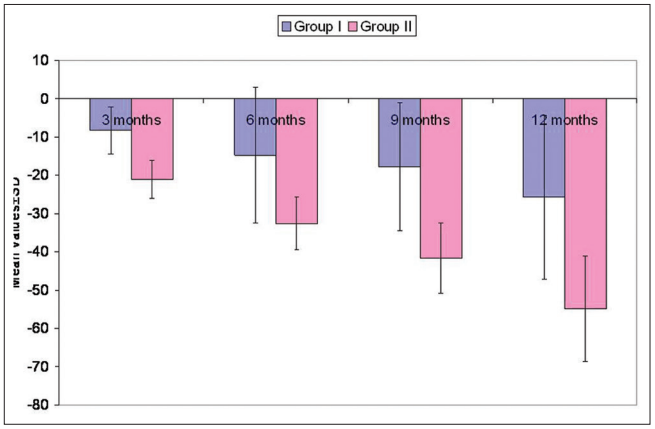

Figure 3: Comparison of % change in microalbuminuria. The percentage reduction from baseline at the end of 1-year in Group II was greater than in Group I (percentage reduction of −54.88% vs. −25.68%, $P < 0.001$)

Table 4: Data related to adverse events

Adverse events	Group I (ACE inhibitor)	Group II (ACE inhibitor and cilnidipine)
Nausea/vomiting	4	5
Hypotension	1	2
Skin reaction	0	0
Palpitation	3	2
Deranged liver function test	2	2
Deranged kidney function tests	2	1
Edema	2	3
Stroke	0	0
Myocardial angina	0	0
Death	0	0

ACE: Angiotensin-converting enzyme

during the course of study between the two groups. Thedose of enalapril used in Group I was 5 ± 2.5 and 5 ± 2.1 in Group II, while thedose of cilnidipine used in Group II was 10 ± 3.

Discussion

Globally diabetes mellitus has emerged as the commonest cause of end stage renal disease. It is the etiological factor in 20–40% of all ESRD patients. Microalbuminuria (30–300 mg albumin/24 h) is a well-known predictor of poor renal outcomes in patients with type 2 diabetes.[8-15] Microalbuminuric patients with type 2 diabetes if left untreated, almost invariably progress to macroalbuminuria and overt diabetic nephropathy.

Although there are various classes of drugs to treat microalbuminuria, we compared monotherapy (enalapril) with combination therapy (enalapril and cilnidipine) to find out whether both are similarly effective or one is better than another in reduction of microalbuminuria. In our study, combination regimen of enalapril and cilnidipine (Group II) was more effective in reducing microalbuminuria than enalapril alone (Group I). In Group I microalbuminuria was reduced by 25.68%, while in Group II there was reduction of 54.88%, which was significant.

Katayama *et al*. also conducted a similar trial in patients with type II diabetes with microalbuminuria. The patients were randomized into two groups to receive either valsartan (an ARB) or valsartan plus cilnidipine for 1-year. After 1-year, microalbuminuria was found to have decreased more in the valsartan plus cilnidipine group (−44 ± 11%) than in the valsartan group (−9 ± 7%).[16]

The antiproteinuric action of ACE inhibitor and its superiority over L-type CCB is supported by a trial conducted by Remuzzi *et al*.[17] over hypertensive patients with type-2 diabetes and normal urinary albumin excretion rate. The study showed that diabetic nephropathy can be prevented by ACE inhibitor therapy and combination of ACE inhibitor with non-dihydropyridine calcium channel blocker (verapamil) does not provide any protective effect over kidney against the development of microalbuminuria.[17]

Our study while confirming ACE inhibitors as agents preventing diabetic nephropathy, also endorses a better improvement in proteinuria by using ACE inhibitor and cilnidipine (dihydropyridine L/N type calcium channel blocker) in combination than ACE inhibitor alone. Fujita *et al.* also supported the use of ACE inhibitor with cilnidipine rather than amlodipine. They conducted a trial over hypertensive patients with chronic kidney disease who were already receiving ACE inhibitor. They were randomly assigned to cilnidipine and amlodipine. Though the difference in reduction of BP between the two groups was not significant, patients treated with cilnidipine showed more decrease in proteinuria than those treated with amlodipine.[7] Hatta *etal*. also observed that in chronic kidney disease patients, cilnidipine has antihypertensive effects equivalent to amlodipine, but proteinuria was reduced by shifting from amlodipine to cilnidipine.[18] Kojima *etal*. also did a study in 28 proteinuric hypertensive patients. One group was kept on amlodipine and other on cilnidipine. The amlodipine group showed a significant increase in proteinuria, while the increase was suppressed in the cilnidipine group.[19] Tanaka conducted his trial in over 25 diabetic patients with hypertension who were on treatment with CCB other than cilnidipine. Medication was changed to cilnidipine, and there was a significant decrease in urinary albumin/creatinine ratio after 3 months of the new treatment.[20] Zaman and Kumari also compared the effects of cilnidipine and amlodipine over BP, heart rate, proteinuria and lipid profile in hypertensive patients. They found that both drugs significantly reduced BP. There was decrease in pulse rate, urinary protein excretion and serum triglyceride in diabetic patients in cilnidipine group.[21]

It is interesting to note that while scores of studies mentioned above including ours and many others have utilized the level of albuminuria as a determinant for progression of diabetic kidney disease and different group of drugs having antiproteinuric effect are widely studied to observe reduction in albuminuria as mark of improvement, some recent studies, including VA Nephron D and subgroup analysis of ALTITUDE trial and bardoxelone trials have shown that albuminuria is not a good surrogate marker for diabetic kidney disease.[22-24]

eGFR instead is suggested as a better alternative. However, these observations need large multicentric trials and their meta-analysis before questioning and writing off albuminuria, which is so far an established surrogate marker widely used presently in determining the state of progression of diabetic kidney disease in clinical practice and research.

Whether these recent developments may have some impact or not, which might be apparent in the time to come, our study focused on microalbuminuria and its levels observed after therapeutic intervention with antiproteinuric agents as determinant for progression of diabetic kidney disease. The results of our study indicate greater reduction in level of microalbuminuria by utilizing both ACE inhibitor and cilnidipine together than ACE inhibitor alone. This combination also appear to leading to greater reduction in proteinuria as compared to a combination of ARB with cilnidipine.[16] As ACE inhibitors are established agents to reduce proteinuria in type-1 diabetics, this combination therapy of ACE inhibitor (enalapril) with cilnidipine may be equally successful in hypertensive albuminuric type-1 and type-2 diabetics together.[25,26] While indicating combination therapy to be better than ACE inhibitor alone, the study prefers ACE inhibitor over an ARB in combination with cilnidipine in treatment of diabetic nephropathy.

Limitations of the study

The main drawback of our study was that it was a single center, open-labeled randomized trial conducted over a small number of patients. Duration of the study was also short to comment on its cardiovascular and renal benefits.

So a large scale, multicenter, double-blind clinical trial involving a larger number of patients for a longer duration will be needed in future to evaluate the effectiveness and superiority of combination therapy over monotherapy in reduction of microalbuminuria and cardiovascular risk.

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