Original Research Article

# To evaluate effect of Olmesartan versus Cilnidipine on urinary microalbumin level in patients of hypertension with type II diabetes mellitus

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## Abstract

**Introduction:** Hypertension can lead to many complications of diabetes, including diabetic eye disease and kidney disease, or make them worse. Most people with diabetes will eventually have high blood pressure, along with other heart and circulation problems.**Materials and Methods:** This is prospective and observational study conducted in Department of pharmacology. Patients were enrolled into study after fulfilling the specified inclusion and exclusion criteria. Patients were divided into 2 groups, Group A received Tab Olmesartan 20mg, Group B received Tab Cilnidipine 10mg. Patients were assessed at baseline and after 3 months for Urinary Microalbumin level and Blood sugar – fasting and post meal.**Result:** In our study, it is seen that after 3 months of therapy, by applying paired 't' test, there is statistically highly significant reduction in microalbuminuria in the two groups. In group A, mean reduction was 22.71 mg, in group B mean reduction in microalbuminuria was 16.69 mg. Whereas by applying Unpaired 't' test for microalbuminuria after 3 months therapy in group A and B, statistically highly significant difference has been observed in both the groups in reducing microalbuminuria ($p < 0.0001$). **Conclusion:** Cilnidipine is equally effective as Olmesartan in reducing blood pressure in hypertensive patients with type 2 DM. However, cilnidipine is more effective in the prevention of albuminuria and better tolerated by patients as compared with Olmesartan.

**Key words:** Olmesartan, Cilnidipine Urinary microalbumin, Hypertension, Type II diabetes mellitus.



## Introduction

Hypertension is common among patients with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors. [1] Furthermore, hypertension is a strong risk factor for atherosclerotic cardiovascular disease (ASCVD), heart failure, and microvascular complications. [2] The worldwide prevalence of diabetes in 2000 was approximately 2.8% and is estimated to grow to 4.4% by 2030. This translates to a projected rise of diabetes from 171 million in 2000 to well over 350 million in 2030. [3] There is considerable evidence for an increased prevalence of hypertension in diabetic persons. In a large prospective cohort study that included 12,550 adults, the development of type 2 diabetes was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts. [4]Microalbuminuria is an early sign of diabetic nephropathy and is associated with incident cardiovascular events. [5] It has been well known that tight blood pressure control with antihypertensive medications targeting the renin-angiotensin system (RAS) can delay the deterioration of renal function and protect against cardiovascular events in patients with type 2 diabetes (T2D) and microalbuminuria. [6]Angiotensin II receptor antagonists (ARBs) confer protection in patients with renal insufficiency, delaying progression in patients with managed hypertension. Most reported cases have been in patients with diabetic mellitus (DM) and related kidney disease. [7] The Reduction of

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Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist trial reported that drug conferred significant renal benefits in patients with type 2 diabetes and nephropathy. [8] However, chronic renal failure is not only DM related, but also occurs in other conditions, such as chronic glomerular nephritis and hypertensive nephrosclerosis, and the number of patients with these conditions is equal to the number of patients with DM-related kidney disease. [9] Cilnidipine is a dual L-/N-type CCB and a previous study demonstrated that cilnidipine treatment significantly reduces urinary protein excretion compared with amlodipine treatment in patients with chronic kidney disease and hypertension receiving an RAS blocker. [10] Therefore, this study aimed to compare the anti-albuminuric effect of the L-/N-type CCB cilnidipine with Olmesartan in patients with T2D and hypertension. In addition, we tried to determine whether cilnidipine has more favourable effects on glucose tolerance, lipid parameters and endothelial function compared with Olmesartan

**Rationale of the study**

Diabetic nephropathy is a serious secondary complication of diabetes mellitius, leading to increased morbidity and mortality, impaired quality of life in person affected. Early detection of the disease, at the stage of microalbuminuria, is important of its outcome and progression. If appropriate measures are taken, microalbuminuria can be halted or even reversed.

**Materials and Methods**

This is prospective and observational study conducted in department of pharmacology in collaboration with department of medicine and Pathology. Patients were enrolled into study after fulfilling the specified inclusion and exclusion criteria.

**Inclusion criteria:**

- Newly diagnosed patients of type II Diabetes Mellitus with Hypertension.
- Blood pressure ≥140/90 mmHg.
- Patients having microalbuminuria.

**Exclusion criteria:**

- Secondary hypertension.
- Patients with history of Type I DM
- Patients with history of liver and renal disease.
- Patients with history of Gastrointestinal Tract diseases (IBD).

Patients were divided into 2 groups and each group has contain 35 patients :

- Group A received Tab Olmesartan 20mg.
- Group B received Tab Cilnidipine 10mg

Patients were assessed at baseline and at the end of 12 weeks drug therapy:

- Urinary Microalbumin level
- Blood sugar – fasting & post meal.

**Statistical analysis**

- Data analysed in Statistical Package for the Social Sciences (SPSS) version 25th was applied.
- A paired 't' test was applied for same group/within group.
- An unpaired 't' test was applied for two groups.
- p value <0.05 indicates Statistically significant.

**Result**

In table 1, total of 70 patients with hypertension and Type 2 diabetes mellitus were eligible patients were randomized equally into two treatment groups. In group A 35 patients and in group B 35 patients were enrolled. Both the groups were similar in demographic profile at baseline as shown in table 1.

**Table 1: Distribution of gender of the subjects by Using Fisher's exact test**

| Gender | Group A | Group B | p - value |
|---|---|---|---|
| **Male** | 19 (54.2) | 20 (57.1) | **0.785** |
| **Female** | 16 (45.7) | 15 (42.8) | |
| **Total** | **35** | **35** | |

**Table 2: Distribution of Age group of the subjects under study**

| Age Group in years | Group A | Group B |
|---|---|---|
| 30-40 | 8 | 7 |
| 40-50 | 11 | 13 |
| 50-60 | 16 | 15 |
| **Total** | 35 (100%) | 35 (100%) |

In table 2, maximum number of patients were between 50-60 years of age group in both Group A and B. Least number of patients were between 30-40 years of age group in Group A and B.

**Table 3: Analysis of microalbuminuria values before and after drug therapy by Paired "t" test**

| Group | | Mean ± SD (mg) | Mean Difference ± SD (mg) | P value |
|---|---|---|---|---|
| Group A | Baseline | 105.74 ± 13.43 | 16.69± 4.06 | <0.0001** |
| | After 3 months | 89.05 ± 9.37 | | |
| Group B | Baseline | 106.36 ± 14.54 | 22.71± 5.22 | <0.0001** |
| | After 3 months | 83.65 ± 9.32 | | |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001-Highly Significant**]

In table 3, it is seen that after 3 months of therapy, by applying paired 't' test, there is statistically highly significant reduction in microalbuminuria in the two groups. In group A, mean reduction was 22.71 mg, in group B mean reduction in microalbuminuria was 16.69 mg.

**Table 4: Intergroup Comparison of microalbuminuria between the groups by Unpaired 't' test**

| | z value | P Value |
|---|---|---|
| **Group A vs B** | 6.452 | <0.0001** |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001 - Highly Significant**]

In table 4, shows that, by applying Unpaired 't' test for microalbuminuria after therapy in group A and B, statistically highly significant difference has been observed in both the groups in reducing microalbuminuria (p <0.0001).

**Table 5: Analysis of systolic blood pressure values before and after drug therapy by paired "t" test**

| Group | | Mean ± SD (mmHg) | Mean Difference ± SD(mmHg) | P value |
|---|---|---|---|---|
| Group A | Baseline | 158.12 ± 7.32 | 19.8 ± 1.31 | <0.0001** |
| | After 3 months | 138.32 ± 6.01 | | |
| Group B | Baseline | 157.43 ± 7.43 | 17.69 ± 1.89 | <0.0001** |
| | After 3 months | 139.74 ± 5.56 | | |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001 - Highly Significant**]

In table 5, in both group were analysed applying by paired t test, highly significant reduction in systolic BP was observed in both the groups after 3 months of therapy.

**Table 6: Intergroup comparison of systolic blood pressure after therapy between the groups by Unpaired 't' test**

| | Z -value | P Value |
|---|---|---|
| **Group A vs B** | 1.871 | 0.863 |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001 - Highly Significant**]

In the table 6, by applying Unpaired 't' test for systolic BP after 3 months of therapy in group A and B, statistically not significant difference has been observed in both the groups in reducing systolic BP (p>0.05).

**Table 7: Analysis of diastolic blood pressure before and after drug therapy by paired "t" test**

| Group | | Mean ± SD (mmHg) | Mean Difference ± SD(mmHg) | P value |
|---|---|---|---|---|
| Group A | Baseline | 99.32 ± 4.75 | 13.08 ± 1.10 | 0.001** |
| | After 3 months | 86.24 ± 3.65 | | |
| Group B | Baseline | 99.61 ± 4.64 | 16.88 ± 1.28 | 0.001** |
| | After 3 months | 82.73 ± 3.36 | | |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001 - Highly Significant**]

In table 7 by applying paired t test, there was statistically highly significant decrease in diastolic BP was observed in both the groups after 3 months of therapy.

**Table 8: Intergroup comparison of diastolic blood pressure after therapy between the groups by Unpaired 't' test**

| | z-value | P Value |
|---|---|---|
| **Group A vs B** | 3.836 | <0.05 |

[P >0.05 – Not Significant, P <0.05 – Significant*, P < 0.001 - Highly Significant**]

In table 8, by applying Unpaired 't' test for diastolic BP after 3 months of therapy in group A and B statistically significant decrease in diastolic BP was observed intergroup comparison after 3 months of therapy (p<0.05).

**Discussion**

Many clinical trials have recommended that the use of ARBs such as Olmesartan slows the progression of diabetic nephropathy and it is commonly used as an antihypertensive drug in patients with essential hypertension with type 2 DM, although the use of ARBs alone for this purpose is not enough and is often prescribed with hydrochlorothiazide.[11]Olmesartan frequently causes hyperkalemia, dry cough, rashes, and rarely angioedema-like severe ADRs in patients. [12]

Contrary to this, some studies have suggested that ARBs are not efficacious to prevent the development of macroalbuminuria (≥300 mg/day urinary albumin) in hypertensive patients with type 2 DM having microalbuminuria (≤30–300 mg/day urinary albumin). [13]However, cilnidipine, a third generation dihydropyridine, CCB is vasoselective and is a dual blocker of L-type and N-type calcium channels. L-type calcium channel blockade produces vasodilation of peripheral resistance vessels. Inhibition of neuronal N-type calcium channels disrupts sympathetic nervous outflow, lowering plasma catecholamine levels, and produces vasodilation of both pre- and post-capillary resistance vessels, reducing capillary hypertension and consequent hyperfiltration of fluid into the interstitium. [14] These dual mechanisms of cilnidipine explain both the low incidence of ankle edema and antihypertensive action without the reflex tachycardia. Cilnidipine effectively prevents the development of diabetic nephropathy and cardiovascular diseases in hypertensive patients with type 2 DM. [15]In our study showed the treatment outcomes of total 70 patients of hypertension with type 2 DM treated with cilnidipine and Olmesartan for 3 months. At the end of 3 months, all patients had significant clinical improvement and decreases of parameters. There were more male (63.9%) than female (36.1%) in our study. Similar observation was observed in a study carried out by Ohishi M et al. [15] On the other hand in our study maximum age group of patients in both cilnidipine- and Olmesartan-treated groups was 50-60 years. Whereas, another study shows that increase in the mean age observed in a study conducted by Lavermann GD et al., in which mean age for ARBs was 61.7 years and for CCBs 66.8 years. [16]

In our study administration of Olmesartan for 3 months decreased the level of microalbumin in urine. The difference between parameter was statistically highly significant (p<0.001). Our results correlate to study conducted by Pedrinelli R et al. revealed that significant decrease in urine microalbumin levels. [17] In our study, we also found that administration of Cilnidipine for 3 months, decreased the level of microalbumin in urine. The difference between parameter was statistically highly significant (p<0.001). These results were comparable to study conducted by Uchida S et al which had concluded that, Cilnidipine is effective in improving albuminuria and drug of choice for diabetic hypertensive patients with hypertension. [18] Another study conducted by Tanaka M, have shown that Cilnidipine has renoprotective effect by lowering urine microalbumin levels in patients having hypertension with type II DM. [19]A parallel improvement in was noted in the present study. Similar results were observed in studies conducted by Forman JP et al. [20] There was a significant (p<0.0001) improvement in albuminuria in patients treated with cilnidipine and Olmesartan in our study after 3 months therapy.

However, in the present study, reduction in urinary albumin in patients treated with cilnidipine was more than in patients treated with Olmesartan. This may be due to dual blockade of cilnidipine on L-type and N type of calcium channels which produces vasodilation of both pre -and post-capillary resistance vessels, reducing capillary hypertension and consequent hyperfiltration of fluid into the interstitium. In addition to this, cilnidipine decreases plasma Angiotensin 2 (AT2) and aldosterone level. Olmesartan is a selective antagonist of AT1 receptor and does not completely block the effect of AT2, which continues to produce albuminuria, especially in patients of NIDDM with hypertension. Similar results were observed in studies conducted by Takashi M et al. [21]

**Conclusion**

Both cilnidipine and losartan are efficacious and safe in patients with essential hypertension and type 2 DM. However, cilnidipine is more efficacious in the prevention of albuminuria in hypertensive patients with type 2 DM and does not cause potassium imbalance. Losartan is associated with more ADRs such as hyperkalemia, dizziness, and dry cough.

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