ORIGINAL RESEARCH

To assess the impact of Olmesartan compared to Cilnidipine on urinary microalbumin levels in patients diagnosed with hypertension and type II diabetes mellitus

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ABSTRACT

Aim: The aim of this study is to assess the impact of Olmesartan compared to Cilnidipine on urinary microalbumin levels in patients diagnosed with hypertension and type II diabetes mellitus. **Materials and Methods:** This study included individuals who were recently diagnosed with type II Diabetes Mellitus and also had hypertension, with a blood pressure equal to or greater than 140/90 mmHg. Additionally, patients with microalbuminuria were also included in the study. A total of 100 patients were allocated into two groups, with each group consisting of 50 patients. Group I received Tab Olmesartan 20mg and Group II received Tab Cilnidipine 10mg**. Results:** In Group I, the average reduction in microalbuminuria was found to be 17.43±2.32 mg, while in Group II, the average reduction was 23.03±2.34 mg. The findings indicate a significant decrease in systolic blood pressure in both groups following a 6-month therapy period. A statistically significant decrease in diastolic blood pressure in both groups after a 6-month therapy period, as determined through the application of a paired t-test. **Conclusion:** Both cilnidipine and Olmesartan have been found to be effective and well-tolerated in individuals diagnosed with essential hypertension and type 2 diabetes mellitus.

Keywords: Olmesartan, Cilnidipine, urinary microalbumin, hypertension, type II diabetes mellitus

INTRODUCTION

The occurrence of hypertension is frequently observed in individuals diagnosed with diabetes, and its prevalence is influenced by various factors such as the type and duration of diabetes, age, gender, race/ethnicity, body mass index (BMI), history of glycemic control, and the existence of kidney disease, among other determinants. In addition, it is important to note that hypertension is a significant contributing factor to the development of atherosclerotic cardiovascular disease (ASCVD), heart failure, and microvascular complications. The global incidence of diabetes in the year 2000 was approximately 2.8%, and projections indicate that it is expected to increase to 4.4% by the year 2030. This projection indicates that the prevalence of diabetes is expected to increase from 171 million in 2000 to more than 350 million by the year 2030. [1] A substantial body of evidence supports the notion that individuals with diabetes exhibit a higher incidence of hypertension. The findings of a substantial prospective cohort study, involving a total of 12,550 adults, revealed that individuals with hypertension were nearly 2.5 times more prone to developing type 2 diabetes compared to those without hypertension. Microalbuminuria serves as an initial indication of diabetic nephropathy and is linked to the occurrence of cardiovascular events. The efficacy of antihypertensive medications that specifically target the RAS in achieving tight blood pressure control has been widely recognized. This approach has been shown to effectively delay the decline of renal function and provide cardiovascular

protection for individuals diagnosed with type 2 diabetes (T2D) and microalbuminuria. Angiotensin II receptor antagonists (ARBs) have been found to provide a protective effect in individuals with renal insufficiency, leading to a delay in disease progression among patients with well-controlled hypertension. The majority of reported cases have been observed in individuals diagnosed with diabetic mellitus (DM) and its associated kidney disease. The diminished renal advantages in individuals diagnosed with type 2 diabetes and nephropathy have been observed [4]. Chronic renal failure is not solely associated with diabetes mellitus, but also manifests in other conditions such as chronic glomerular nephritis and hypertensive nephrosclerosis. The prevalence of chronic renal failure in these non-diabetes-related conditions is comparable to that observed in diabetes-related kidney disease. [6]

Cilnidipine is a CCB that exerts inhibitory effects on both the L-type calcium channel and the N-type calcium channel. Cilnidipine has been found to effectively reduce the excessive release of catecholamine and suppress reflective tachycardia in hypertensive patients when compared to amlodipine. This is attributed to the abundant expression of the N-type calcium channel in peripheral sympathetic nerve endings. Furthermore, a recent study has demonstrated that inhibitors of L-type calcium channel blockers (CCBs) specifically dilate the afferent arteries of glomeruli, while leaving the efferent arteries unaffected. On the other hand, cilnidipine, a medication that inhibits N-type calcium channels, has been found to dilate both the afferent and efferent arteries. This observation suggests that N-type calcium channel inhibition may play a role in reducing glomerular hypertension and preventing proteinuria. The study demonstrated that cilnidipine exhibited a more pronounced efficacy compared to amlodipine in mitigating the advancement of proteinuria among individuals with hypertension.[6]

Cilnidipine is a calcium channel blocker that acts on both L-type and N-type calcium channels. A previous study has provided evidence that cilnidipine treatment leads to a significant decrease in urinary protein excretion when compared to amlodipine treatment. This effect was observed in patients with chronic kidney disease and hypertension who were also receiving a renin-angiotensin system (RAS) blocker. [7] Hence, the objective of this study was to assess and compare the efficacy of the L-/N-type calcium channel blocker cilnidipine and the angiotensin II receptor antagonist olmesartan in reducing albuminuria in patients diagnosed with type 2 diabetes and hypertension. Furthermore, our study aimed to assess the potential superiority of cilnidipine over Olmesartan in terms of its impact on glucose tolerance, lipid parameters, and endothelial function.

MATERIALS AND METHODS

This study is a prospective and observational investigation conducted within the department of pharmacology. This study included individuals who were recently diagnosed with type II Diabetes Mellitus and also had hypertension, with a blood pressure equal to or greater than 140/90 mmHg. Additionally, patients with microalbuminuria were also included in the study. The study excluded individuals diagnosed with secondary hypertension, individuals with a medical history of Type I diabetes mellitus, individuals with a medical history of liver and renal disease, and individuals with a medical history of gastrointestinal tract diseases, specifically inflammatory bowel disease (IBD). A total of 100 patients were allocated into two groups, with each group consisting of 50 patients.

- Group I received Tab Olmesartan 20mg
- Group II received Tab Cilnidipine 10mg

Urinary Microalbumin level and Blood sugar level were assessed at baseline and at the end of 6 weeks drug therapy.

STATISTICAL ANALYSIS

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 25. A paired t-test was utilized to analyze data within the same group. A two-sample t-test was conducted to compare the means of two independent groups. A p-value that is less than 0.05 is indicative of statistical significance.

RESULT

Table 1 presents the distribution of 100 eligible patients diagnosed with hypertension and Type 2 diabetes mellitus, who were randomly assigned in equal numbers to two treatment groups. A total of 50 patients were enrolled in Group I, while an equal number of 50 patients were enrolled in Group II.

Table 1: Distribution of age and gender

Gender	Group I		Group II		p - value
	Number	Percentage	Number	Percentage	
Male	27	54	29	58	0.19
Female	23	46	21	42	
Age					0.52
Below 35	11	22	10	20	
35-45	15	30	17	34	
Above 45	24	48	23	46	

The majority of patients in both Group I (48%) and Group II (46%) were aged above 45 years. The proportion of patients below the age of 35 was the lowest in Group 1 (22%) and Group II (20%).

Table 2: Microalbuminuria values before and after drug Treatment

	Group I	Group II	Group I VS Group II
	Mean ±SD	Mean ±SD	Z value (P value)
Baseline	106.41 ± 7.51	107.14 ± 6.85	7.25(0.001)
After 6 months	88.98 ± 5.19	84.11 ± 4.51	
Mean Difference	17.43±2.32	23.03±2.34	
P value	0.001	0.001	

Table 2 displays the results of the paired 't' test conducted after a 6-month therapy period, indicating a statistically significant reduction in microalbuminuria within both groups. In Group I, the average reduction in microalbuminuria was found to be 17.43±2.32 mg, while in Group II, the average reduction was 23.03±2.34 mg. Table 2 presents the results of an Unpaired 't' test conducted to assess the impact of therapy on microalbuminuria in groups I and II. The analysis reveals a statistically significant difference in the reduction of microalbuminuria in both groups ($p = 0.001$).

Table 3: Systolic blood pressure values before and after drug Treatment

	Group I	Group II	Group I VS Group II
	Mean±SD (mmHg)	Mean±SD (mmHg)	Z value (P value)
Baseline	159.11 ± 8.14	158.24 ± 8.11	1.52(0.29)
After 6 months	139.41 ± 7.03	140.11 ± 6.14	
Mean Difference	19.70 ±1.11	18.13±1.97	
P value	0.001	0.001	

Table 3 presents the results of the paired t-test analysis conducted on both groups. The findings indicate a significant decrease in systolic blood pressure in both groups following a 6-month therapy period. In Table 3, the application of an Unpaired 't' test was used to analyze the systolic blood pressure after a 3-month therapy period in groups I and II. The results indicate that there is no statistically significant difference in the reduction of systolic blood pressure between both groups ($p>0.05$).

Table 4: Diastolic blood pressure before and after drug therapy

	Group I	Group II	Group I VS Group II
	Mean±SD (mmHg)	Mean±SD (mmHg)	Z value (P value)
Baseline	98.85 ± 5.14	98.97 ± 5.24	2.55 (0.44)
After 6 months	85.96 ± 3.14	81.96 ± 3.22	
Mean Difference (mmHg)	12.89±2.0	17.01±2.02	
P value	0.001	0.001	

Table 4 demonstrates a statistically significant decrease in diastolic blood pressure in both groups after a 6-month therapy period, as determined through the application of a paired t-test. Table 4 demonstrates the results of an Unpaired 't' test conducted to analyze the diastolic blood pressure (BP) after a 6-month therapy period in groups I and II. The findings indicate a statistically significant reduction in diastolic BP when comparing the two groups after the 6-month therapy period ($p<0.05$).

DISCUSSION

Olmesartan exhibits antagonistic properties towards the angiotensin II receptor. Through this mechanism, it effectively regulates blood pressure in patients with both diabetes and hypertension. Multiple clinical trials have been conducted to compare the efficacy of olmesartan with other angiotensin receptor blockers (ARBs), revealing that olmesartan demonstrates superior effectiveness in terms of controlling blood pressure and reducing microalbuminuria. Numerous clinical trials have provided recommendations regarding the utilization of angiotensin receptor blockers (ARBs), such as Olmesartan, for the purpose of decelerating the advancement of diabetic nephropathy. Additionally, Olmesartan is frequently employed as an antihypertensive medication in patients diagnosed with essential hypertension and type 2 diabetes mellitus. However, it is important to note that the utilization of ARBs alone is insufficient for this purpose, and it is often prescribed in combination with hydrochlorothiazide. Olmesartan has been observed to commonly induce hyperkalemia, dry cough, rashes, and infrequently, angioedema-like severe adverse drug reactions (ADRs) in patients. [8]

In contrast, certain studies have indicated that angiotensin receptor blockers (ARBs) may not be effective in preventing the progression of macroalbuminuria (defined as urinary albumin levels of ≥300 mg/day) in hypertensive patients with type 2

diabetes mellitus who already have microalbuminuria (defined as urinary albumin levels of ≤30–300 mg/day). [9]Nevertheless, cilnidipine, which belongs to the third generation of dihydropyridine calcium channel blockers (CCBs), exhibits vasoselectivity and acts as a dual antagonist for both L-type and N-type calcium channels. The inhibition of L-type calcium channels results in the dilation of peripheral resistance vessels. The disruption of sympathetic nervous outflow through the inhibition of neuronal N-type calcium channels results in the reduction of plasma catecholamine levels. This, in turn, leads to the vasodilation of both pre- and post-capillary resistance vessels. Consequently, there is a decrease in capillary hypertension and the subsequent hyperfiltration of fluid into the interstitium. The low occurrence of ankle edema and absence of reflex tachycardia can be attributed to the dual mechanisms of cilnidipine. [10] Cilnidipine has been shown to be an effective preventive measure against the onset of diabetic nephropathy and cardiovascular diseases in individuals with hypertension and type 2 diabetes mellitus. In this study, we examined the treatment outcomes of a cohort of 100 patients diagnosed with hypertension and type 2 diabetes mellitus. These patients were treated with cilnidipine and Olmesartan for a duration of 6 months. After a duration of 6 months, it was observed that all patients experienced notable clinical improvement and a reduction in various parameters. The study revealed a higher proportion of male participants (56%) compared to female participants (44%). A study conducted by Ohishi M et al. yielded a comparable finding. [15] The majority of patients in both Group I (48%) and Group II (46%) were aged above 45 years. The proportion of patients below the age of 35 was found to be the lowest in Group 1 (22%) and Group II (20%). In contrast, a separate study conducted by Lavermann GD et al. revealed an observed rise in the average age. Specifically, the mean age for individuals receiving ARBs was found to be 61.7 years, while those receiving CCBs had a mean age of 66.8 years. According to our study, the administration of Olmesartan for a duration of 6 months resulted in a reduction in urinary microalbumin levels. The observed disparity between the parameters exhibited a statistically significant level of significance ($p<0.001$). The findings of our study align with those of Pedrinelli R et al., which demonstrated a noteworthy reduction in urine microalbumin levels. In the present study, it was observed that the administration of Cilnidipine over a period of six months resulted in a reduction in urinary microalbumin levels. The observed disparity between the parameters exhibited a statistically significant level of significance ($p<0.001$). The findings of this study were found to be similar to a previous study conducted by Uchida S et al, which concluded that Cilnidipine is an effective treatment for improving albuminuria in diabetic hypertensive patients with hypertension.[14] A separate investigation carried out by Tanaka M demonstrated that Cilnidipine exhibits renoprotective properties by reducing urine microalbumin levels in individuals diagnosed with hypertension and type II diabetes mellitus. [15] The present study observed a concurrent enhancement. Forman et al. (year) reported comparable findings in their conducted studies. [16] Our study found a statistically significant improvement in albuminuria ($p<0.0001$) among patients who received treatment with cilnidipine and Olmesartan for a duration of 6 months.

Nevertheless, the current study observed a greater decrease in urinary albumin levels among patients receiving cilnidipine compared to those receiving Olmesartan. The observed phenomenon can potentially be attributed to the simultaneous inhibition of cilnidipine on both L-type and N-type calcium channels. This dual blockade results in the dilation of both pre- and post-capillary resistance vessels, thereby reducing capillary hypertension and subsequently decreasing the excessive filtration of fluid into the interstitium. Furthermore, cilnidipine has been shown to reduce plasma levels of Angiotensin 2 (AT2) and aldosterone. Olmesartan functions as a specific antagonist of the AT1 receptor, while not fully inhibiting the activity of AT2. Consequently, AT2 remains active and contributes to the development of albuminuria, particularly in patients with non-insulin dependent diabetes mellitus (NIDDM) and hypertension. The studies conducted by Takashi M et al. yielded comparable findings. [17]

CONCLUSION

Both cilnidipine and losartan have been found to be effective and well-tolerated in individuals diagnosed with essential hypertension and type 2 diabetes mellitus. Nevertheless, cilnidipine demonstrates greater efficacy in the prevention of albuminuria among hypertensive patients diagnosed with type 2 diabetes mellitus, while also avoiding the occurrence of potassium imbalance. The administration of Losartan has been found to be correlated with an increased occurrence of adverse drug reactions (ADRs), including hyperkalemia, dizziness, and dry cough.

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