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COMPARATIVE STUDY OF EFFECT OF OLMESARTAN AND CILNIDIPINE ON MICRO ALBUMINURIA LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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INTRODUCTION

The International Diabetic Federation estimated that in 2015, the prevalence of diabetes from ages 20 to 79 years was 8.8%.[1] By the year 2030, it is estimated that India will be having 79.4 million diabetic patients and 439 million adults will be affected in the world (corresponding to 7.8% of the world's adult population).[2] Chronic long term microvascular and macrovascular tissue complications are one of the most important clinical features associated with diabetes. The major causative factor in initiating organ damage is duration and severity of hyperglycemia.[3] For small blood vessels in organs like kidney, eyes and nerves to get affected, it almost takes 15 years. The kidney is the most important target of microvascular damage in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM).[4,5] It has been observed that almost 20 to 40% of diabetic patients are at the risk of developing chronic kidney disease (CKD).[5]

KEYWORDS: term microvascular and macrovascular.

During the initial 10 to 20 years after onset of diabetes the average incidence of diabetic nephropathy is high (3% per year).[6] Diabetic nephropathy (DN) has emerged as a leading cause of the end stage renal disease.[7] DN is a multi-stage condition that takes several years to become clinically overt. There are usually changes in renal function such as glomerular hyperfiltration, increased renal blood flow and hypertrophy of the kidney. Most of these changes can be reversed at an early stage by good glycemic control, but they persist in many patients and may be important in the later development of clinical nephropathy.[8] Appearance of low but abnormal levels =30 mg/day of albumin in the urine, referred to as microalbuminuria is the earliest clinical evidence of nephropathy considered clinically as incipient nephropathy.[6] Even when renal function is normal or only slightly impaired hypertension is an early feature in the course of persistent proteinuria,[7] Previously known as diabetic nephropathy, Diabetic Kidney Disease (DKD) is the new medical term introduced in 2007 by the Kidney Disease Outcomes Quality Initiative (KDOQI).[9]

It has been observed that the occurrence of hypertension is approximately twice as common in persons with diabetes as in those without diabetes [10] The overlap between hypertension and diabetes significantly increases the risk of vascular complications and rate of[11] renal deterioration. It has been suggested that the increasing systemic arterial BP might be transmitting a higher pressure to the glomerular and peritubular capillaries (in the presence of afferent arteriolar dilation), thereby promoting abnormal glomerular selectivity or changes in tubular albumin processing[11] Persistent hyperglycemia in type II diabetes is responsible for glomerular hyper-filtration and initiates a cascade of inflammation, oxidative damage, fibrosis, and activation of the rennin – angiotensin - aldosterone system (RAAS).[3] In patients with DKD and those with stage 3 or 4 chronic kidney disease with proteinuria the deterioration in the renal function has been attributed to over-activity of the renin–angiotensin system.[4] Angiotensin converting enzyme inhibitors(ACEIs) and angiotensin receptor blockers (ARB) have been observed to play an important role in the reduction of the risk of progression of microalbuminuria to macroalbuminuria[5] and eventually to DKD.[3] DN remains an important clinical problem even after incorporating therapies for intensive glycemic and antihypertensive control and thus the need for newer therapeutic agents for prevention and treatment of this condition becomes an essential priority.[10]

Because of their proven reno-protective effects angiotensin converting enzyme inhibitors (ACE Inhibitors) and angiotensin receptor blockers are the first

line drugs considered to be used in treatment of hypertension with diabetes mellitus. Recently, their beneficial effects of reduction in proteinuria have been more emphasized.[12] But the renoprotective benefits of these agents are overshadowed by the incidence of adverse drug reactions like dry cough, hyperkalemia and angioedema,[13] ARBs have been more efficacious in reducing blood pressure as well as microalbuminuria as compared to any other conventional antihypertensive therapies according to the large-scale clinical trials conducted in hypertensive type 2 diabetic patients with microalbuminuria.[14] Olmesartan is an angiotensin II type 1 receptor blocker, most commonly used in treatment of hypertension with diabetes mellitus, for preventing or delaying the development of microalbuminurea and diabetic kidney disease. Several clinical trials comparing olmesartan to other ARBs have proven that Olmesartan has been more efficacious in controlling blood pressure & microalbuminurea.[15]

Calcium channel blockers (CCBs) is another class of antihypertensive drugs. CCBs are one of the most widely used agents which prevent target organ damage by decreasing blood pressure in diabetic hypertensive patients. A dihydropyridine derivative CCB Cilnidipine not only inhibits the L-type calcium channel, but also the N-type calcium channel, there by causing vasodialation of both the afferent and efferent arterioles and exerting renoprotective effect.[16] In multiple trials when compared with other CCBs , cilnidipine was shown to have a superior effect in preventing the progression of proteinuria in hypertensive patients [17] Also, cilnidipine has shown the highest impact on reducing renin-angiotensin system activation.[17] Olmesartan and Cilnidipine, both have proven their efficacy to reduce urinary microalbumin level. But as on date no head to head studies comparing effect of Cilnidipine versus Olmesartan on urinary microalbumin level in diabetic hypertensive patients have been conducted. Considering this background, present study was planned to compare and evaluate safety and efficacy of Olmesartan and Cilnidipine, on microalbuminuria levels in patients with type II diabetes mellitus with hypertension.

MATERIAL AND METHODS

3 months prospective, open label, single center, double arm, interventional, clinical study, was conducted at MGM Medical College, Aurangabad in collaboration with Department of Medicine in newly diagnosed patients of diabetes with hypertension aged between 30 to 60 years (N= 60) Inclusion criteria was patients of either sex (male or female) having microalbuminuria with HbA1c < 8% and Blood pressure ≥140/90 mmHg.. Patients with Secondary hypertension, Bronchial asthma, Chronic obstructive pulmonary disease, Hepatic or renal disease were not included. Patients having overt albuminurea, Cardiovascular co-morbidities, Pregnant or lactating women, those with known allergy to drugs were excluded. Smokers, tobacco chewers and alcoholic patients were also excluded from the study.

All the patients participating in the study were explained clearly about the purpose and nature of the study in the language they can understand. They were included in the study only after obtaining a written informed consent form (ICF).

Following the approval of the Institutional Ethics Committee the study was initiated. All information pertaining to the patient visiting Out Patient Department, such as patient's age, gender, occupation, relevant history, past history and drug therapy given will be recorded in a Case Record Form (CRF). Details of the prescribed drugs for Diabetes mellitus, and all other drugs used in the patient during treatment were recorded. They include the dose, duration, type of dosage form used, frequency of drug administration etc. and necessary information was recorded in a structured CRF.

Study assessment was done by evaluating the study visit checklist which included informed consent, screening for inclusion criteria & exclusion criteria, general & physical examination. Blood sugar – fasting & post prandial , glycosylated hemoglobin level (HbA1C) , ECG SGOT, SGPT KFT Urinary Microalbumin level , serum Creatinine level and blood pressure with safety assessment were performed at baseline and follow-up visit . Total 2 visits were planned. First visit at the baseline and Second visit at 3 months, at the end of the study. In between patients were evaluated at end of first and secnd month for: General and Clinical examination and possible ADR of study drugs.

Patients were randomly divided into two groups of 30 each.Patients in the GROUP I were prescribed with Tab Olmesartan 20mg OD and those in the GROUP II received Tab Cilnidipine 10mg OD . Material kit used for the test of Microalbuminurea Urine-Albumin was measured using a rapid *in vitro* test manufactured by NycoCard® U-Albumin kit for measurement of low albumin concentrations in human urine.

Primary end point was change in microalbuminuria levels from baseline up to 3 months. Secondary end point was change in blood pressure from baseline up to 3 months. Safety assessment was performed by general and systemic examination and as per ADR reported by patients. The study was performed on 60 patients of which 38 were males and 22 were females. Data was collected at the baseline, and at the end of 3 months for estimation of FBS, PPBS, HbA1c value and UACR, ECG, SGOT, SGPT and blood pressure. Paired t test was applied to the data within the two groups and unpaired t test was applied to compare the data between the two groups and result was derived by using SPSS v.24

RESULTS

The study was performed on 60 patients of which 36 were males and 24 were females. Among 60 patients recruited in the study were divided in two study groups with 30 patients enrolled in group I and the remaining 30 were recruited in group II. Patients in the group I were prescribed with tab. Olmesartan 20 mg OD and those in group II received tab. Cilnidipine 10 mg OD. In group I 17 patients (56.7%) were males and 13 (43.3%) were females .The average age of patients enrolled in group I was 48.03 ± 7.97 years. In the group II there were 19 (63.3%) males and 11 (36.7%) females. (Figure 1) (Table 1). The average age of patients in group II was 46.70 ± 7.84 years. After 3 months of study, 17.414 mg % reduction was observed in the urinary albumin levels from baseline in group I and 13.034 mg % reduction was recorded , in group II (P value< 0.0001). All the 60 patients in both the groups tolerated Olmesartan 20 mg and Cilnidipine 10 mg once daily well. In this study, at 3 months, The mean urinary albumin (in mg/dl) in group I at baseline was 105.62 ±36.309 , at the end of 3 months it was 88.207± 32.495 . (Figure 2) A highly Significant reduction was recorded in the values of urinary albumin with mean difference of – 17.414 from baseline to the end of 3 months (P< 0.0001) (Table 2). The mean systolic blood pressure (in mm of Hg) in group I at baseline was 158.345±7.965, and at the end of study it was observed to be 148.138± 6.885. (Figure 3) A significant reduction was recorded in the values of systolic blood pressure with mean difference of – 10.207 from baseline to the end of therapy (P< 0.0001) (Table 3). In group I Olmesartan treated patients the mean diastolic blood pressure (in mm of Hg) at baseline was recorded to 98.138 ±4.068 , which was reduced to 90.414 ± 3.397 at the end of study (Figure 4) with a significant mean difference of – 7.724 (P< 0.0001)(Table 4). So within the group I where the 30 patients received Olmesartan tablet 20 mg OD a highly significant reduction with (P < 0.0001) was observed within the group at the end of 3 months in all the parameters. In the group II where patients were prescribed with tab. Cilnidipine 10 mg OD therapy a statistically highly significant reduction was observed in the values of all the parameters within the group. The mean urinary albumin (in mg/dl) in this group at baseline was 107.172 ±38.708, and at the end of 3 months it was 94.138± 34.004. (Figure 5) A highly Significant reduction was recorded in the values of urinary albumin with mean difference of – 13.034 from baseline to the end of study (P< 0.0001)(Table 5). The mean systolic blood pressure (in mm of Hg) in Cilnidipine receiving group at baseline was 160.552±9.117, and at the end of study it was observed to be reduced to 150.00± 8.159. (Figure 6) A significant reduction was recorded in the values of systolic blood pressure with mean difference of – 10.552 from baseline to the end of therapy (P< 0.0001) (Table 6). In this group the mean diastolic blood pressure (in mm of Hg) at baseline was recorded to 98.966 ±4.888, which was reduced to 90.138 ± 4.340 at the end of study (Figure 7) with a significant mean difference of – 8.828 (P< 0.0001) (Table 7). So within the group II where the 30 patients were prescribed with tablet Cilnidipine 10 mg OD a highly significant reduction with (P < 0.0001) was observed within the group at the end of 3 months in all the parameters.

From the above results , a statistically highly significant reduction with (P<0.0001) was observed in all the parameters such as urinary albumin levels , systolic & diastolic blood pressure from the baseline at the end of 3 months in Olmesarten treated group I and Cilnidipine treated group II individually . But when we compared the after therapy results of both the groups with each other observations were different. At the end of 3 months the difference in the mean values of urinary albumin levels between group I and Group II was -5.931mg/dl (figure 8) with (P = 0.5) (Table 8) which was not significant . Similarly the difference in the mean values of systolic blood pressure between both the groups was also non significant with P = 0.352 (Table 9) with a mere difference of -1.862 mm of Hg (Figure 9). A negligible difference of only 0.276 mm of Hg was observed in the diastolic blood pressure (Figure 10) where reduction in Cilnidipine treated group was more as compared to group I with a P value of 0.788 (table 10) which is statistically non significant . Hence though there was a more reduction in the values of urinary albumin levels and systolic blood pressure in Olmesartan treated group I as compared to Cilnidipine treated group at the end of 3 months of study, it was not statistically significant.

Table 01: Values of urinary albumin levels (in mg%) at subsequent visits.

Group I Olmesartan Therapy Group			
Baseline value 105.62 ±36.309 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	88.207± 32.495	17.414	P< 0.0001

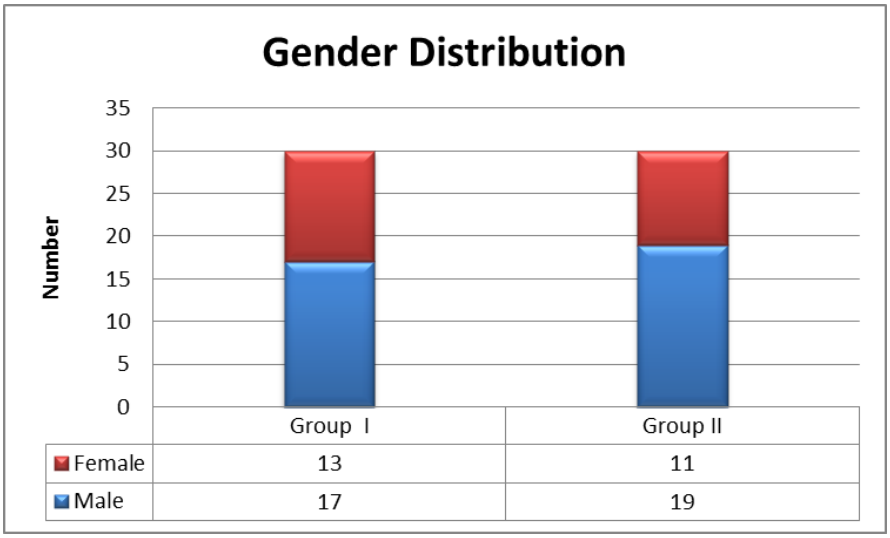

Figure 1: Showing gender wise distribution among Group I and Group II.

Table 02: Values of Systolic Blood Pressure (mm of Hg) at subsequent visits.

Group I Olmesartan Therapy Group			
Baseline value 158.345±7.965 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	148.138± 6.885	10.207	P< 0.0001

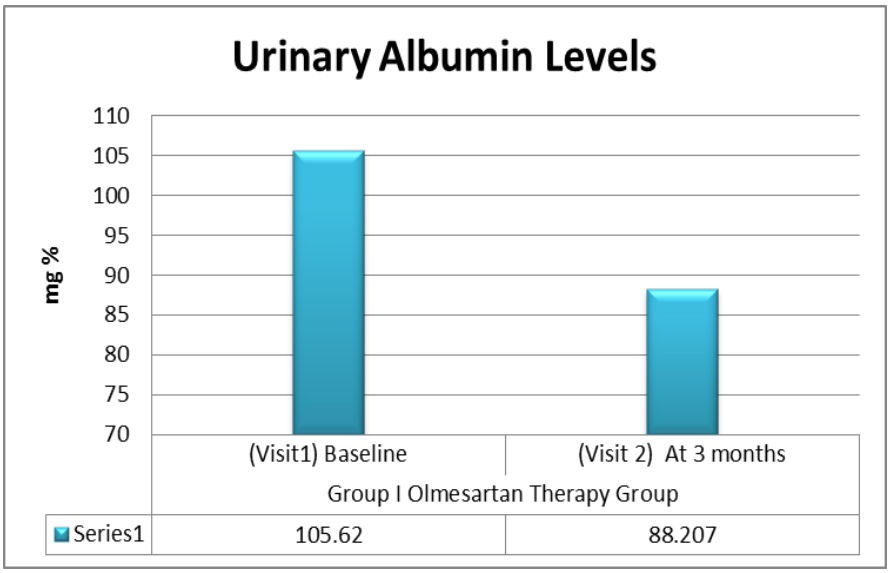

Figure 2: Showing changes in mean urinary albumin levels from baseline to subsequent visit.

Table 03: Values of Diastolic Blood Pressure (mm of Hg) at subsequent visits.

Group I Olmesartan Therapy Group			
Baseline value 98.138 ±4.068 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	90.414 ± 3.397	7.724	P< 0.0001

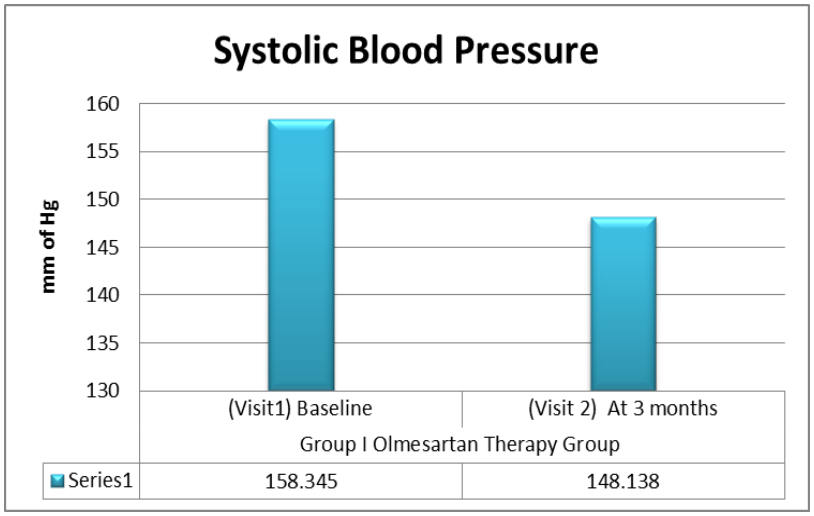

Figure 3: Showing changes in mean systolic blood pressure from baseline to subsequent visit.

Table 04: Values of urinary albumin levels (in mg%) at subsequent visits.

Group II Cilnidipine Therapy Group			
Baseline value 107.172 ±38.708 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	94.138± 34.004	13.034	P< 0.0001

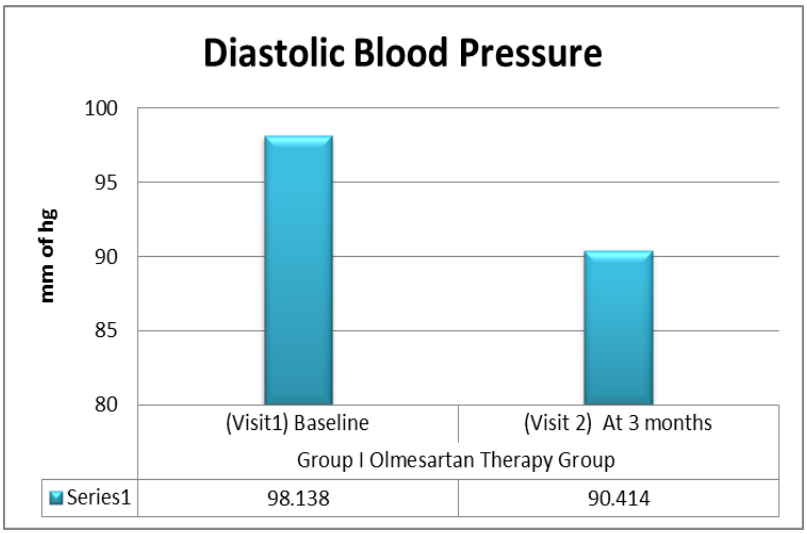

Figure 4: Showing changes in mean diastolic blood pressure values from baseline to subsequent visit.

Table 05: Values of Systolic Blood Pressure (mm of Hg) at subsequent visits.

Group II Cilnidipine Therapy Group			
Baseline value 160.552±9.117 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	150.00± 8.159	10.552	P< 0.0001

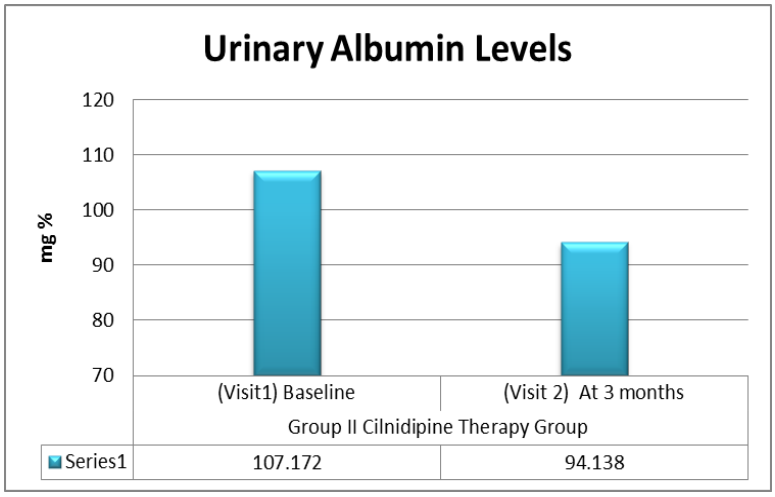

Figure 5: Showing changes in mean urinary albumin levels from baseline to subsequent visit.

Table 06: Values of Diastolic Blood Pressure (mm of Hg) at subsequent visits

Group II Cilnidipine Therapy Group			
Baseline value 98.966 ±4.888 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	90.138 ± 4.340	8.828	P< 0.0001

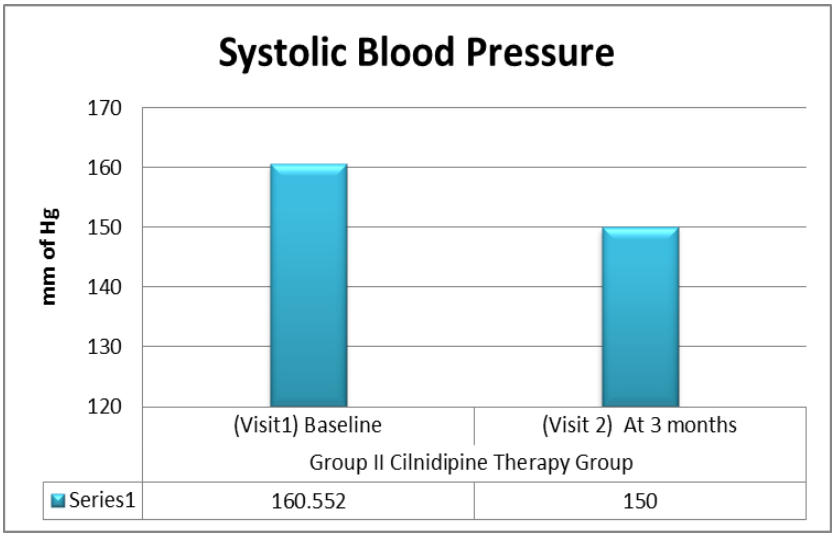

Figure 6: Showing changes in mean systolic blood pressure values from baseline to subsequent visit.

Table 06: Values of Diastolic Blood Pressure (mm of Hg) at subsequent visits

Table 07: Group II Cilnidipine Therapy Group			
Baseline value 98.966 ±4.888 (Visit 1)			
Number of visits	Mean+ SD (Standard Deviation)	Mean difference	P value
(Visit 2) At 3 months	90.138 ± 4.340	8.828	P< 0.0001

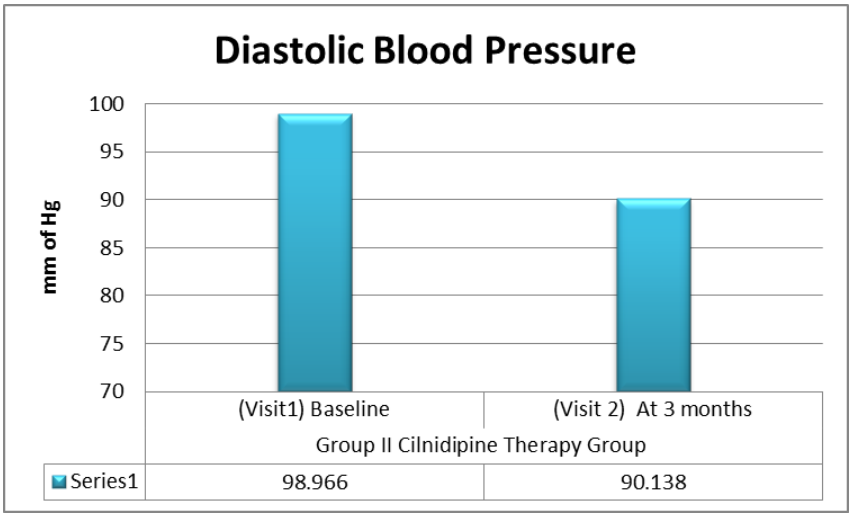

Figure 7: Showing changes in mean diastolic blood pressure values from baseline to subsequent visit.

Table 08: Comparative Values of urinary albumin levels (in mg%).

Group I Olmesartan Therapy	Group II Cilnidipine Therapy		
Mean+ SD	Mean+ SD	Mean difference	P value
88.207± 32.495	94.138± 34.004	-5.931	P = 0.5

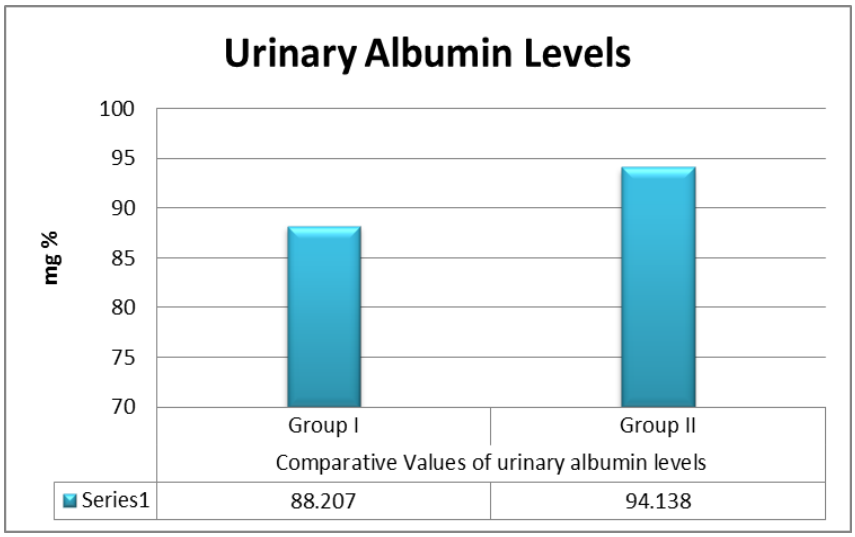

Figure 8: Showing comparative values of urinary albumin levels in both groups at the end of study.

Table 09: Comparative Values of Systolic Blood Pressure (mm of Hg).

Group I Olmesartan Therapy	Group II Cilnidipine Therapy		
Mean+ SD	Mean+ SD	Mean difference	P value
148.138 ± 6.885	150.00 ± 8.159	-1.862	P = 0.352

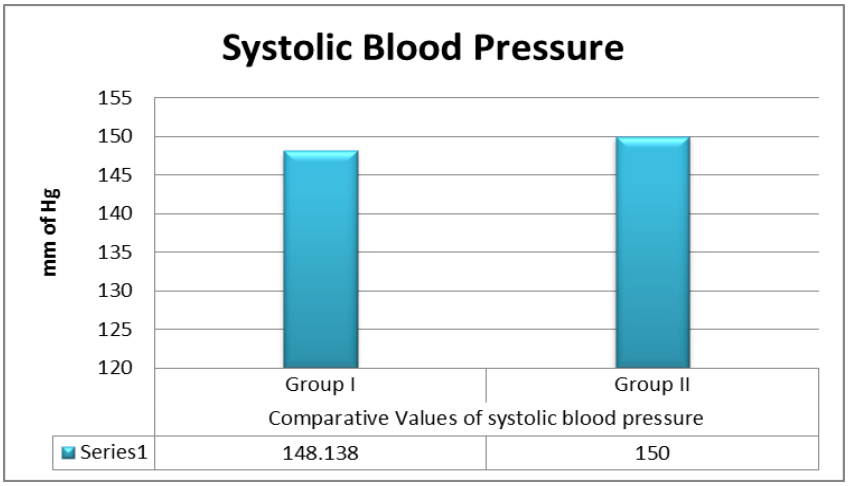

Figure 9: Showing comparative values of systolic blood pressure in both groups at the end of study.

Table 10: Comparative Values of Diastolic Blood Pressure (mm of Hg).

Group I Olmesartan Therapy	Group II Cilnidipine Therapy		
Mean+ SD	Mean+ SD	Mean difference	P value
90.414 ± 3.397	90.138 ± 4.340	0.276	P = 0.788

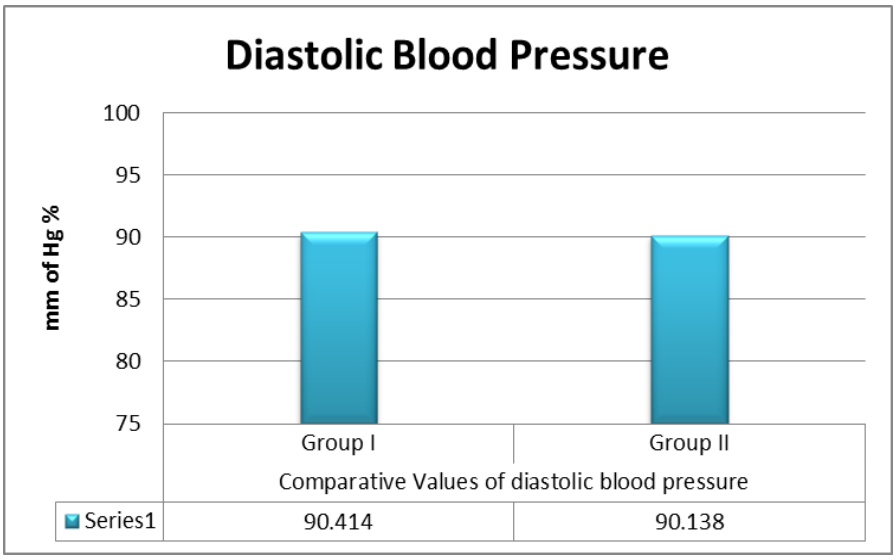

Figure 10: Showing comparative values of diastolic blood pressure in both groups at the end of study.

DISCUSSION

One of the important microvascular complications of uncontrolled diabetes is Diabetic Nephropathy (DN) eventually leading to end stage renal disease if not addressed properly.[4] Persistent hyperglycemia results in deleterious structural changes and functions of kidney.[5] Appearance of albumin in the urine (microalbuminuria) (30-300 mg/dl), is the first sign of diabetic nephropathy.[4] It may progress to macroalbuminuria or overt nephropathy (>300 mg/dl). Once overt nephropathy occurs, the GFR gradually falls over a period of time leading to cause End Stage Renal Disease. Around 20 – 40 % of type II DM patients with microalbuminuria progress to overt nephropathy. [7] Thus annual monitoring of urinary microalbumin is essential for screening of diabetic nephropathy. Glomerular and tubular hypertrophy, increased thickness of glomerular basement membranes, proliferation of mesangial cells, changes in vascular cells and progressive accumulation of extracellular matrix components are some of the pathological changes, eventually leading to proteinuria and renal failure in DN.[8]

It has been suggested that generally there is a correlation between high blood pressure and microalbuminuria.[10] Even high normal blood pressure is associated with significant higher frequency of microalbuminuria and thus an indicator of of increased cardiovascular risk. Role of common genetic factors that predispose to both high BP and microalbuminuria has also been considered.[6] It is possible that the development of microalbuminuria may mark the onset of pathophysiologic events that aggravate BP or impair the

response to the BP-lowering effects of antihypertensive drugs alternatively,[12]

Haemodynamically mediated damage to the glomerulus is attributed to dialation of afferent arteriole which is an early effect of systemic hypertension.[12] In DN increased intraglomerular pressure which is responsible for renal injury is due to alteration in the rennin-angiotensin function. ARB inhibitors provide protection from glomerular damage by reducing efferent arterial pressure, and by decreasing intraglomerular pressure. [14]

Cilnidipine is a CCB that inhibits not only the L-type calcium channel, but also the N-type calcium channel. As the N-type calcium channel is abundantly expressed in peripheral sympathetic nerve endings[16] cilnidipine reduces excessive release of catecholamine and suppresses reflective tachycardia in hypertensive patients.[16] In addition, A recent study showed that the L-type CCB inhibitors dilate only afferent arteries of glomeruli; whereas cilnidipine dilates both the afferent and efferent arteries, suggesting that N-type calcium channel inhibition seems to attenuate glomerular hypertension and prevent proteinuria.[17]

Several studies have shown that Olmesartan and Cilnidipine decrease microalbuminurea and delay progression to macroalbuminurea or overt nephropathy. A total of 60 patients of type II DM with hypertension having microalbuminurea were enrolled, and divided into two groups. Each group included 30 patients. Group I received tab Olmesartan 20 mg OD and group II received tab CIlnidipine 10 mg OD for 3 months. Among the patients enrolled in group I, the mean value of urinary albumin (in mg/dl) at baseline was 105.62 ±36.309 and 3 months after therapy it was 88.207± 32.495 . A highly Significant reduction was recorded in the values of urinary albumin with mean difference of – 17.414 from baseline to the end of the study (P< 0.0001) Highly significant reduction was also observed in systolic and diastolic blood presseure (in mm of Hg) with mean difference of – 10.207 and of – 7.724 respectively from baseline to the end of therapy (P< 0.0001) in Olmesartan treated group I patients with (P< 0.0001). Our results were similar to the study conducted by Herman Haller et al. [18] which demonstrated, significant decrease in urine microalbumin levels with olmesartan . Similar highly significant reduction was also observed in Cilnidipine treated group II patients where a mean difference of– 13.034 mg/dl , – 10.552 and– 8.828 in mm of Hg was respectively observed in urinary albumin levels and systolic and diastolic blood pressure from baseline to the end of therapy (P< 0.0001) Our result was comparable with the study conducted by Uchida S et al[19] which concluded that, Cilnidipine is the drug of choice for diabetic hypertensive patients due to its effective role in improving albuminurea. Tanaka M in their study also observed that Cilnidipine has renoprotective effect by lowering urine microalbumin levels in patients having hypertension with type II DM.[20] Therefore by application of paired t test individually within group I with Olmesartan treated patients & Cilnidipine treated group II (Before & after the therapy) we observed a statistically highly significant ($p<0.001$) reduction in the in the values of all the parameters. But when we compared the after therapy results of the two groups by applying unpaired t test ,we observed that the difference in the mean values of urinary albumin levels and systolic and diastolic blood pressure were-5.931mg/dl with ($P = 0.5$) , -1.862 mm of Hg ($P = 0.352$) and 0.276 with a P value of 0.788 in mm of Hg respectively between group I and group II which was non significant.

Multiple Large-scale Clinical trials conducted in type 2 Diabetic hypertensive patients with microalbuminuria have shown that, angiotensin II, type 1 receptor blockers (ARBs) are more effective in reducing blood pressure as well as microalbuminuria than any other conventional antihypertensive therapies.[14]

Olmesartan is an angiotensin II type 1 receptor blocker that smoothly controls blood pressure in diabetic hypertensive patients, It is most commonly used in treatment of hypertension with diabetes mellitus, for prevention or delay of development of microalbuminurea and diabetic kidney disease. Clinical trials have established the superiority of olmesartan as compared to other ARB s in terms of blood pressure control & microalbuminurea.[15] Beneficial effects of olmesartan in delaying the microalbuminurea along with smooth control of blood pressure have been proved by A ROADMAP trial.[21]

A superior effect of cilnidipine on proteinuria than amlodipine in 50 hypertensive patients was observed in a research conducted by Konoshita et al in 2011.[22] Also, Cilnidipine was proven to have the highest impact on reducing renin-angiotensin system activation.[17] A significant reduction in urinary microalbumin level with Cilnidipine as a monotherapy has been observed in a study conducted by *Fujita T et al* (J-CIRCLE Study).[19,23] But, no significant reduction in urinary microalbumin level with Cilnidipine was studied in a research conducted by *Katsuayuki A et al.* (SAKURA).[24]

SUMMARY AND CONCLUSION

In present study, both the drugs Cilnidipine and Olmesartan as monotherapy reduced not only microalbuminuria levels but also blood pressure levels significantly after 3 months of therapy. Though there was a more reduction in the values of urinary albumin levels and systolic blood pressure in Olmesartan treated group I as compared to Cilnidipine treated group at the end of 3 months of study, it was not statistically significant. The results of our study revealed that Olmesartan and Cilnidipine produced promising effects by reducing microalbuminuria levels along with smooth control of blood pressure in diabetic hypertensive patients by

imparting better renoprotection in them. Both the drugs established their potential to prevent or prolong the renal complication of diabetes. In our study we found that the antihypertensive drug Olmesartan and cilnidipine have better efficacy and safety in the control of hypertension as well as favorable effects on microalbumine levels. Thus from this study we can conclude that Olmesartan and Cilnidipine both molecules help in better control of hypertension and prevention of long term morbidity and mortality in diabetic patients due to stroke, CAD and diabetic kidney disease.

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