ejpmr, 2020,7(10), 521-527

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COMPARATIVE EFFECT OF CILNIDIPINE, OLMESARTAN ALONE AND IN COMBINATION ON URINARY MICRO-ALBUMIN LEVEL IN PATIENTS OF TYPE 2 DIABETES MELLITUS WITH HYPERTENSION

Dr. Rajesh Kadam, Dr. Deepak Bhosle*, Dr. Jyoti Bobde, Dr. Bhakti Chandekar and Dr. Snehal Chavan

India.

***Corresponding Author: Dr . Deepak Bhosle**

Department of Pharmacology, MGM Medical College Aruangabad a constituent unit of MGMIHS Navi Mumbai.

Article Received on 04/08/2020 **Article Revised on 24/08/2020** **Article Accepted on 14/09/2020**

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that causes hyperglycemia due to total or subtotal deficiency of insulin along with component of insulin resistance. Persistent hyperglycemia in diabetes if not controlled adequately is known to cause various long term microvascular (Diabetic nephropathy, retinopathy and Peripheral neuropathy), macrovascular (coronary artery diseases, peripheral vascular diseases, and cerebrovascular accidents) and acute metabolic complications (Diabetic ketoacidosis, hyperglycemic hyperosmolar coma and hypoglycemia). Several distinct types of diabetes exist like Type I diabetes, Type II diabetes, Type 1.5 diabetes and Gestational diabetes which are caused by a complex interaction of genetics and environmental factors.[1][2]

In type II diabetes persistent hyperglycemia causes glomerular hyper-filtration and triggers inflammation, oxidative damage, fibrosis, and activation of the rennin - angiotensin - aldosterone system (RAAS).[3] Over-activity of the renin-angiotensin system has been implicated in the deterioration of renal function in patients with diabetic nephropathy and in patients who have stage 3 or 4 chronic kidney disease with proteinuria.[4] Angiotensin converting enzyme inhibitors and angiotensin receptor blocker have been shown to reduce the risk of progression of microalbuminuria to microalbuminuria[5] and to diabetic nephropathy.[3]

Hypertension affects approximately 70% of patients with diabetes and is approximately twice as common in persons with diabetes as in those without diabetes.[6] The prevalence of coexistent hypertension and diabetes varies across different ethnic, racial, and social groups. The overlap between hypertension and diabetes substantially increases the risk of microvascular and macrovascular complications[7] Importantly, hypertension in patients with diabetes causes a significant increase in the risk of vascular complications in this population, and together both conditions predispose to chronic kidney disease.[8,9]

Diabetic nephropathy (DN) is one of the most important microvascular complications associated with type II diabetic patients and has emerged as a leading cause of the end stage renal disease[10] and rate of renal deterioration are most closely related to the patient's blood pressure and hyperglycemia. The first sign of diabetic nephropathy is the appearance of albumin in the urine (microalbuminuria).[11] DN is characterized by structural abnormalities of kidney including hypertrophy of both glomerular and tubular elements, increase in the thickness of glomerular basement membranes, and progressive accumulation of extracellular matrix components, eventually leading to proteinuria and renal failure.[12] Despite implementation of intensive glycemic and antihypertensive control, DN remains an important clinical problem[10] and creating the need for newer therapeutic agents for prevention and treatment of this condition.

Angiotensin converting enzyme inhibitor (ACE Inhibitors) and angiotensin receptor blocker are the first line drugs to be used in treatment of hypertension with diabetes mellitus because of their proved renoprotective effect. Recently, there has been a focus on the beneficial effects of reduction in proteinuria[13] But incidence of adverse drug reactions like dry cough, hyperkalemia and angioedema, have barred the renoprotective benefits of these agents.[14]

Large-scale clinical trials in hypertensive type 2 diabetic 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.[15]Olmesartan is an angiotensin II type 1 receptor blocker, most commonly used in treatment of hypertension with diabetes mellitus, for prevention or delay of development of microalbuminuria and diabetic kidney disease.

Olmesartan antagonizes action of angiotensin II receptor. By this mechanism, it smoothly controls blood pressure in diabetic hypertensive patients. Several clinical trials comparing olmesartan to other ARB shows more efficacy of olmesartan in terms of blood pressure control &microalbuminuria.[16] A "ROADMAP" trial conducted to evaluate renoprotective effect of olmesartan, shows that olmesartan is beneficial or effective in delaying the microalbuminuria along with smooth control of blood pressure.[17]

Calcium channel blockers (CCBs) are one of the most widely used antihypertensive drugs to decrease blood pressure in diabetic hypertensive patients for prevention of target organ damage. Cilnidipine is a dihydropyridine derivative CCB that acts on both L & N type calcium channels, causing substantial vasodilatation of both the afferent and efferent arterioles and showing renoprotective action.[18] The efficiency of cilnidipine in humans has been extensively compared to similar CCBs. Multiple trials on patients have shown clear benefit of cilnidipine administration compared to amlodipine. A research conducted by Konoshita et alin 2011 on 50 hypertensive patients revealed a stronger effect of cilnidipine on proteinuria than amlodipine.[19]Also, cilnidipine has the highest impact on reducing renin-angiotensin system activation.[20] The effect is most important with respect to the reflex activation of the RAAS induced by other antihypertensive therapies like ACE inhibitors or ARBs.[21] A study conducted by *Fujita T et al* (J-CIRCLE Study) has shown that there is significant reduction in urinary microalbumin level with Cilnidipine as a monotherapy[22,23] But, a study conducted by *Katsuayuki A et al* (SAKURA) exhibited no significant reduction in urinary microalbumin level with Cilnidipine.[24]

Olmesartan and Cilnidipine, both are known to reduce urinary microalbumin level, as on date there are no head to head studies comparing effect of Cilnidipine versus Olmesartan on urinary microalbumin level in diabetic hypertensive patients. Considering this background, present study was planned to evaluate safety and efficacy of Cilnidipine, Olmesartan alone and in combination on urinary microalbumin level in diabetic hypertensive patients.

MATERIAL AND METHODS

Patient selection

Present study was conducted in department of pharmacology in collaboration with department of medicine and Pathology, MGM Medical College & Hospital, Aurangabad. The patients enrolled for this study were selected from the Out-Patient Department of medicine, MGM medical College, Aurangabad. The study was approved by institutional ethics committee (MGM-ECRHS, Aurangabad). Patients were enrolled into study after fulfilling the specified inclusion and exclusion criteria.

Inclusion criteria

- Patients of either gender between age group 30 to 60 years.
- Patients willing to participate in the study and give written informed consent.
- Newly diagnosed patients of type II Diabetes Mellitus with Hypertension.
- Patients having microalbuminuria.
- HbAlc< 8 %.
- Blood pressure >140/90 mmHg.

Exclusion criteria

- Secondary hypertension.
- Patient having overt albuminuria.
- Bronchial asthma.
- Hepatic or renal disease.
- Cardiovascular co-morbidities.
- Pregnant or lactating women.
- Known allergic to drugs
- Chronic obstructive pulmonary disease.
- Smoker, tobacco chewer and alcoholic patients.

Study design

- 12 weeks randomized open label, single center prospective three arm clinical study
- Study was conducted as per ICH GCP guideline.
- Study was conducted after obtaining permission from institutional ethics committee.
- Total 60 newly diagnosed patients of diabetes with hypertension were enrolled in the study after fulfilling the inclusion criteria.
- Patients were divided into 3 groups and each group has contained 20 patients:
- Group I received Tab Cilnidipine l0mg.
- Group II received Tab Olmesartan 20mg.
- Group III received Tab Cilnidipine l0mg + Tab Olmesartan 20mg.
- Patients were assessed at baseline for the following investigations...
- Urinary Microalbumin level
- Patients were assessed at the end of 12 weeks drug therapy:
- Urinary Microalbumin level
- Possible ADR of study drugs

Drug and dosage:

Groups	Drugs	Dose	Duration
I	Cilnidipine	10 mg OD	12 weeks
II	Olmesartan	20 mg OD	12 weeks
III	Cilnidipine + Olmesartan	10 mg+ 20 mg OD	12 weeks

Study Visits included clinic visits on day 0, day 30, day 60 and day 90.

Patients withdrawn due to an Adverse Event (AE) were supposed to be followed untilthe AEhas abated, or until a stable situation had been reached. All tests/examinations scheduled at study completion were supposed to be performed at premature termination/dropout. Drop outs were supposed to be replaced. All premature discontinuations, reasons and their causes were documented.

Statistical analysis

We used paired "t" test to measuredifferences within group, and ANOVA to measure differences within group and among the group respectively.

RESULTS

The present study was carried out in collaboration with the Department of Medicine, MGM Medical College and Department of Pathology, MGM Medical College, Aurangabad.A total of 60 patients were enrolled.

Patients were randomly divided into three groups of 20 each

- GROUP I: Tab Cilnidipine 10mg OD
- GROUP II :Tab Olmesartan 20mg OD
- Group III: Tab Cilnidipine 10 mg OD+ Tab Olmesartan 20 mg O.D

Table No. 1: Age and Sex wise distribution of the subjects under study.

Age in years	**Group I**		**Group II**		**Group III**	
Gender	M	F	M	F	M	F
30-40	03	02	04	01	02	03
40-50	06	04	02	04	05	05
50-60	03	02	05	04	02	03
TOTAL	12	08	11	09	09	11

Table l: Shows the age and sex wise distribution of the subjects in all groups under study. All the 3 groups consist of 20 subjects each. Group I: Consists of 60% male and 40% female patients,Group II: consists of 55 % male and 45% female and Group III: consists of 45 % male and 55% female patients.

Table No. 2: Analysis microalbuminerea values before and after drug therapy by paired "t" test:

Group		**Mean ± SD**	**Mean Difference** ± SD	P value
GroupI	Baseline	104.05 ±36.759	14.0± 10.728	0.001**
	After 3 months	90.05 ± 34.374		
Group II	Baseline	107.10 ±35.805	20.19± 12.671	0.001**
	After 3 months	86.90 ±31.322		
GroupIII	Baseline	115.71 ±30.208	61.67± 18.725	0.001**
	After 3 months	54.05 ±27.160		

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

From the above table, it is seen that after 3 months of therapy, by applying paired 't* test, there is highly significant reduction in microalbumurea in all the three groups. In group I, mean reduction was 14.0, in group II mean reduction in microalbuminurea was 20.19 whereas mean reduction in group III was 61.67

Table 3:Intergroup Comparison of microalbuminuria among the groups byANOVA.

	F Value	P **Value**
Group I vs II vs III	7.182	**0.001****

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

Above table shows that, by applying ANOVA for microalbuminurea after therapy in group I, II & III, p value was 0.001 which means that the differences in reducing microalbuminureain three groups was highly significant.

Table 4:Intergroup Comparison of microalbuminuria by Unpaired "t" test.

Comparison	**t-value**	**p-value**	**Sign/Not sign**
Group IVsGroup II	0.295	0.77	Not Significant
Group IVsGroup III	3.58	0.001**	Highly Significant
Group IIVsGroup III	3.45	0.001**	Highly Significant

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

Above table shows that by applying unpaired t test for microalbuminuria, no significant difference was observed between group I & II. On other hand, highly significant difference was observed between Group I & Group III. Similarly, intergroup comparison between Group II & III showed highly significant difference.

Table 5: Analysis or systolic blood pressure values before and after drug therapyby paired "t" test:

Group		Mean ± SI)	Mean Difference ± SD	1* value
Group I	Baseline	155.2 ±6.57	11.2 ±3.97	0.001**
	After 3 months	144 ± 6.01		
Group II	Baseline	156.1 ±6.20	10.10 ±4.23	0.001**
	After 3 months	146 ±4.35		
Group III	Baseline	158.1 ±4.83	18.7 ±3.74	0.001**
	After 3 months	139.4 ±3.73		

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

From the above table, it is seen that by applying paired t test, highly significant reduction m systolic BP was observed in the all three groups after 3 months of therapy.

Table 6: Intergroup Comparison of systolic blood pressure after therapy among the groups by ANOVA.

	F Value	P Value
Group I vs II vs III	9.946	**0.001****

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

Above table shows thatby applyingANOVA forsystolic BP after 3 months of therapy in group I, II &III,p-value was 0.001. This means highly significant difference has been observed in all the three groups in reducing systolic BP.

Table 7: Intergroup Comparison of systolic blood pressure between group by Unpaired 't' test.

Comparison	t-value	p-value	Sign/Not sign
Group I Vs Group II	1.20	0.24	Not Significant
Group I Vs Group III	2.91	**0.006****	Highly Significant
Group II Vs Group III	5.15	**0.001****	Highly Significant

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

Above table shows that, by applying unpaired 't' test for systolic BP, no significant difference was observed between group I& II. However, significant difference was 'Served in group I & III and highly significant difference in group II & III.

Table 8: Analysis of diastolic blood pressure before and after drug therapy by paired 't' test.

Group		Mean ± SD	Mean difference ± SD	P value
Group I	Baseline	97.6 ± 3.98	9.1 ±3.14	**0.001****
	After 3 months	88.5 ±3.78		
Group II	Baseline	97.4 ± 2.43	7.0 ± 1.65	**0.001****
	After 3 months	90.4 ± 2.64		
Group III	Baseline	98.1 ±2.63	12.0 ±3.37	**0.001****
	After 3 months	86.1 ±3.81		

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

From the above table, it is seen that by applying paired t test, highly significant reduction in diastolic BP was observed in all the three groups after 3 months of therapy.

Table 9: Intergroup Comparison of diastolic blood pressure after therapy among the groups by ANOVA.

	F Value	P Value
Group I vs II vs III	7.789	**0.001****

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

Above table shows that by applying ANOVA for diastolic BP after 3 months of therapy in group I, II& III, p value was 0.001, this means highly significantdifference has been observed in all the three groups in reducing diastolic BP.

Table l0:lntergroup comparison ofdiastolic blood pressurebetween the groups by unpaired 't' test.

Comparison	t-value	p-value	Sign/Not sign
Group IVsGroup II	1.84	0.07	Not Significant
Group IVsGroup III	**2.00**	0.05*	Significant
Group IIVsGroupIII	4.15	**0.001****	Highly Significant

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

Above table shows that, by applying unpaired t test for diastolic BP, no significant difference was observed between group I & II. However, significant difference was observed in group I & III and highly significant difference in group II & III.

Table l1: Adverse drug reaction of study drugs

	Ankle edema	Dry cough
Cilnidipine	02	00
Olmesartan	00	01
Cilnidipine + Olmesartan	01	00
Total	03	01

DISCUSSION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism due to total or subtotal deficiency of insulin along with component of insulin resistance. Approximately 70% of patients with diabetes have Hypertension and is more common in with diabetes than without diabetes. The co-existence between hypertension and diabetes substantially increases the risk of microvascular and macrovascular complications. In diabetic individuals, hypertension can be defined as blood pressure > 130/90 mmHg with no comorbidity. However, if the factor such as hyperglycemia persists then it leads to accelerated hypertension in diabetic individuals leading to diabetic nephropathy and end stage renal disease if not addressed properly.

There is positive link between high blood pressure and microalbuminuria. High blood pressure may cause microalbuminuria by increasing glomerular filtration pressure and subsequent renal damage. It is possible that the development of microalbuminuria is a marker for pathophysiologic events that aggravate BP or impair the response to the BP- lowering effects of antihypertensive drugs or, alternatively, that the increasing systemic arterial BP transmits 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. Even high normal blood pressure is associated with significant higher frequency of microalbuminuria and this way may be a biomarker of increased cardiovascular risk. There may be also common genetic factors Predispose to both high BP and microalbuminuria.

Diabetic nephropathy is one of the important microvascular complication of uncontrolled diabetes and leading cause of end stage renal disease. Diabetic nephropathy is referred as deleterious structural changes and function of kidney due to persistent hyperglycemia. early changes in diabetic nephropathy is characterized by microalbuminuria (30-300 mg/dl), 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 ESRD. Around 20 - 40 % of type II DM patients with microalbuminuria progress to overt nephropathy. DN is generally associated with hypertension. Dilatation of afferent arteriole is an early effect of systemic hypertension contributes to hyper filtration, intraglomerular hypertension and hemodynamically mediated damage to the glomerulus.

Glomerular hyper filtration early changes in the development of diabetic nephropathy which is leads to GBM damage followed by progressive thickening of basement membrane, proliferation of mesangial cells and pathological changes in vascular cells. Also, formation and accumulation of AGE's which leads to microvascular complications, activation of protein kinase C and accumulation of polyols by the Aldose reductase pathway.

Annual monitoring of urinary microalbumin is essential for screening of diabetic nephropathy. In DN rennin-angiotensin function get altered, causes increased intraglomerular pressure leading to renal injury. ARB inhibitors reduce efferent artery pressure, decreases intraglomerular pressure, and helps in protection of glomerular Similarly Cilnidipine, a L-/N-type calcium channel blocker, blocks the N-type calcium channel, causes inhibition of over activity of sympathetic nerve, results in dilation of both afferent and efferent arterioles of kidney and decreases glomerular pressure.Several studies show that Olmesartan and Cilnidipine decreases microalbuminuria and delays progression to macroalbuminurea or overt nephropathy.

A total of 60 patients of type II DM with hypertension having microalbuminuria were enrolled, and divided into three groups. Each group consists of 20 patients. Group I received tab Cilnidipine 10 mg OD, group II received tab Olmesartan 20 mg OD and group II received tab Cilnidipine 10 mg + tab Olmesartan 20 mg OD for 12 weeks.

Among the group I, mean value of baseline therapy was 104.05 and mean value after 12 weeks therapy was 90.05. In group II, mean value of baseline therapy was 107.10 and mean value after 12 weeks therapy was 86.90 and in group III, mean value of baseline therapy was 115.71 and mean value after 12 weeks therapy was 54.05.

In our present, we found that administration of Cilnidipine for 12 weeks, 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[22] which had concluded that, Cilnidipine is effective in improving albuminuria and drug of choice for diabetic hypertensive patients with hypertension. Another study conducted by Tanaka M[25], have shown that Cilnidipine has renoprotective effect by lowering urine microalbumin levels in patients having hypertension with type II DM.

Similarly, administration of Olmesartan for 12 weeks also decreased the level ofmicroalbumin in urine. The difference between parameter was statistically highly significant ($p<0.001$). Our results correlate to study conducted by Herman Haller et al.[26] revealed, significant decrease in urine microalbumin levels.

Also, combination therapy of Cilnidipine and Olmesartan for 12 weeks there was marked decrease inurine microalbumin levels. The difference between parameter was statistically highly significant ($p<0.001$). This result correlates to a study done by Fujita T et al., concluded that Cilnidipine is more beneficial when combined with a renin-angiotensin system inhibitor. Another preclinical animal study done by Kazi R et al.[27] exhibited thatCCB enhances renoprotective effects of ARB.

Comparison between groups, we found that there is no significant difference between Cilnidipine and Olmesartan treated group of after 12 weeks therapy. Comparison between Cilnidipine vs Combination group as well as Olmesartan vs Combination treated group of 12 weeks therapy, the results are statistically highly significant.

CONCLUSION

In present study, both the drugs Cilnidipine and olmesartan as monotherapy and in combination reduced not only microalbuminuria levels but also blood pressure level significantly after weeks of treatment.

The advantage of using combination therapy seen in Group III as it has reduced urinary microalbumin level to the greater extent. The results of our study reveal that combination of Cilnidipine and Olmesartan produced more pronounced effect on microalbuminuria along with smooth control of blood pressure in diabetic hypertensive patients as compared to monotherapy and enables them better renoprotection and has potential to prevent or prolong the renal complication of diabetes.

In our study, we found that the antihypertensive drug cilnidipine and Olmesartan alone Und in combination has better efficacy and safety in the control of hypertension as well as favorable effects on microalbumine levels. Thus, helps in better control of hypertension and prevention of long term morbidity and mortality in diabetic patients due to stroke, CAD and diabetic kidney disease.

From this study, we can conclude that Cilnidipine and Olmesartan alonehas significantly reduced urinary microalbumin level but more pronounced effect has seen with combination in terms of reducing microalbumin levels and better control of blood pressure.

REFERENCES

1. Vijsy V, Snehalatha C, Ramachandran A, Viswanathan M. Prevalence of proteinuria in non-insulin dependent diabetes. J Assoc Physicians India, 1994; 42: 792- 794.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res ClinPract, 2010; 87(1): 4-14.
3. Choudhury D, Tuncel M, Levi M. Diabetic nephropathy—a multifaceted target of new therapies. *Discov Med*, 2012; 10: 406-15.
4. Lewis E J, Hunsicker L G, Clarke W R, et al. Renoprotective effect of the angiotensin- receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med, 2001; 345: 851-60.
5. Parving H H. Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N EnglJ* Med, 2001; 345: 870-8.
6. Klein R *et al*. The incidence of hypertension in insulin-dependent diabetes. *Arch Intern Med*, 1996; 156: 622-627.
7. Najarian R M *et al*. Metabolic syndrome compared with type 2 diabetes mellitus N Jrisk factor for stroke: the Framingham Offspring Study. *Arch Intern Med, 20*06; 166: 106-111.
8. Wannamethee S G *et al*. Metabolic syndrome vs Framingham Risk Score for fiction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch \enMed*,2005**;** 165**:** 2644-2650.
9. Adler A 1 *et al*. Association of systolic blood pressure with macrovascular and microvascular complications, ot type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*, 2000; 321: 412-419.
10. Gross J, Azevedo M J ,Silveiro S, Canani L, Caramori M, and Zelmanovitz T. "Diabetic nephropathy'.diagnosis, prevention, and treatment," *Diabetes Care*, 2005; 28(1): 164-176.
11. Mogensen C E. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med*, 1984; 310: 356-360.
12. Sego S. "Pathophysiology of diabetic nephropathy," *Nephrology Nursing Journal*, 2007; 34(6): 631-633.
13. Kunz R, Friedrich C, Wolbers M, Mann J F. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the rennin angiotensin system on proteinuria in renal disease. Ann Intern Med, 2008; 148: 30-48.
14. Sadjadi S A, McMillan J I, Jaipaul N, Blakely P, Hline S S. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. TherClin Risk Manag, 2009; 5: 547-552.
15. Ruggenenti P, Fassi A, Ilieva A P, Bruno S, Iliev I P, Brusegan V. BergamoNephrologic Diabetes Complications Trial (BENEDICT) Investigators.eventing microalbuminuria in type 2 diabetes. *N Engl J Med*, 2004; 351: 1941— 1951.
16. Imai M et al. Olmesartan reducing incidence of end stage renal disease in Diabeti Nephropathy Trail (ORIENT): Rational and study design. Hypertens Res, 2006; 29(29).
17. Yoshiyuki H, Koshiyma H. Macgregor Ga, Kaplan Nm. Fast Facts: Hypertension. 3rd Edition Abingdon, Uk : Health Press. Pollock Dm, Pollock Js. Endothelin And Oxidative Stress In The Vascular System. Curr. Vase. Pharmacol, 2005; 3(4): 365-367.

18. Haynes Wg, Webb Dj. Endothelin As A Regulator Of Cardiovascular Function In Health And Disease. J. Hypertens, l998; 16(8): 1081-1098.
19. Kurtz A. Control of Renin Synthesis and Secretion. Am J Hypertens, 2012; 25(8): 83947.
20. Mcconnaughey Mm, McconnaugheyJs, IngenitoAj. Practical Considerations of The Pharmacology Of Angiotensin Receptor Blockers. J ClinPharmacol, 1999; 39: 547-59.
21. ArtomiS, NiinumaK, Ogawa T- Konda T. Nina K. Effects of an N-type calcium aniagorifton angiotensin 11-renin feedback. *Am J Sephrol*, 2011; 33(2): 168-75.
22. Uchida S, Takahashi M. Sugawara M. Saito T. Nakai K. Fujita Met al. Effects of the S/L-Type Calcium Channel Blocker Cilnidipine on Nephropathy and Uric. Metabolism in Hypertensive Patients With Chronic Kidney Disease (J- GIRCLE Study). ClinHypertens (Greenwich), 2014; 16(10): 746-53.
23. Fujita T, Ando K, Nishimura H, Ideura T. Yasuda G et al. Antiproteinuriceffect of channelblocker cilnidipine added to renin-angiotensin inhibition in
24. KatsuayukiA, Ueshima K, Tanaka S, Kosugi S, Sato T et al. Comparison of theantialbuminuricEffects of L-/N-type and L-type Calcium Channel Blockers in hypertensivePatients with Diabetes and Microalbuminuria: The Study of Assessment for kidneyFunction by Urinary Microalbumin in Randomized (SAKURA) Trial. *International Journal of Medical Sciences*, 2013; 10(9): 1209-1216.
25. Tanaka *M.* The L/N-type Calcium Channel Blocker, Cilnidipine, Reduces Heart Rate and Albuminuria in Patients with Type 2 Diabetes. The Journal of H International Medical Research, 2010; 38: 602 - 610.
26. Hermann halier, et al. n Enj Med, 2011; 364: 907-917.
27. Kazi R, ct al. Calcium Channel Blocker Enhances Beneficial Effects of anAngiotensin *II* ATI Receptor Blocker against Cerebrovascular-Renal Injury in type 2 Diabetic Mice.PLOS ONE, 2013; 8(12): 82082.