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Comparative Study of Effect of Enalapril and Telmisartan on Glycosylated Haemoglobin and Liver Function Test in Patients of Diabetic Nephropathy

*Dr Swetha G[1], Dr Deepthi Gorla[2], Dr Ramya Gajam[3]
[1,2,3](MBBS, MD, Dept of Pharmacology, Osmania Medical College, Hyderabad, Telangana, India)
*Corresponding Author: *Dr Swetha G*

Abstract: *Diabetic nephropathy is usually found in persons who have had diabetes for 10-20 years. Numerous physiological and biochemical mechanisms could explain the protective effect of RAS inhibition against the development of type 2 diabetes in individuals with arterial hypertension. An open label, prospective comparative clinical study was conducted in out-patient and in-patient department of Nephrology in Osmania General Hospital to compare the effect of Enalapril and Telmisartan on Glycosylated Haemoglobin and Liver Function Test in 100 patients of Diabetic Nephropathy. They were divided in to two groups of 50 patients of age group 18-65years of either sex. Group A received Enalapril 5mg orally once a day daily for 3 months. Group B received Telmisartan 40mg orally once a day daily for 3 months. HbA1C(%), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP) & bilirubin were done at baseline and after 3 months of treatment. Any adverse effects of the treatment were also recorded. Paired t-test to compare within the group and unpaired t-test for intergroup analysis was used, with level of significance 0.05. Telmisartan is found to have greater efficacy in glycaemic control, equal hepatotoxic effect and lower incidence of adverse effects compared to Enalapril.*

Keywords: *Enalapril, Telmisartan, Diabetic nephropathy, HbA1C, Liver Function Test*

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I. Introduction

Diabetes Mellitus (DM) is a growing worldwide epidemic. Diabetic nephropathy (DN) is one of the most important DM complications, which is the leading cause of kidney disease in patients starting renal replacement therapy and effects nearly 40% of type 1 and type 2 diabetic patients. The rapidly rising incidence of diabetes mellitus (DM) worldwide is reputed to impact over 380 million people[1]. China now has the highest rates of number of people with DM, around 98.4 million, followed by India with 65.1 million and then the USA[2]. DM is the fifth cause of morbidity and mortality worldwide[3] and the most common cause of ESKD in the Western World[4].

Diabetic nephropathy is defined by persistent pathological albuminuria, progressive decline in the glomerular filtration rate (GFR) and elevated blood pressure. Pathological changes develop in the glomeruli of patients with long duration diabetes mellitus before the appearance of microalbuminuria. The increased Renin Angiotensin Aldosterone system (RAAS) activity plays an important role in the hemodynamic and nonhemodynamic pathogenetic mechanisms involved in kidney disease. Dysregulation of the renin-angiotensin-aldosterone system (RAAS) results in progressive renal damage. RAAS blockade is the cornerstone of treatment of DKD, with proven efficacy in many arenas.

Current therapy directed at delaying the progression of diabetic nephropathy includes intensive glycaemic and optimal blood pressure control, proteinuria / albuminuria reduction, interruption of the renin-angiotensin-aldosterone system through the use of angiotensin converting enzyme inhibitors and angiotensin type-1 receptor blockers, along with dietary modification and cholesterol lowering agents[5]. Targeting RAS may lead to alterations in microcirculation and changes in ionic status that potentially could affect both cellular insulin action and islet insulin secretion[6].

Angiotensin-converting enzyme inhibitors (ACEIs) inhibit angiotensin converting enzyme (ACE) and have been shown to be effective in decreasing albuminuria in patients with DM more effectively than other antihypertensive medications. They are the first line drugs that are used for the treatment of hypertension in patients with diabetic Type I nephropathy. Lisinopril, enalapril, benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril are long acting members of the class. All are prodrugs and converted to active agents by hydrolysis primarily in liver[7]. Hepatotoxicity, usually cholestatic in nature, has been reported with captopril, enalapril[8], and Lisinopril use. All of the currently used ACE inhibitors are associated with a low rate of serum enzyme elevations during chronic therapy (0.2% to 2%) which is minimally different from the

rate of elevations during placebo therapy[9]. A number of clinical trials utilizing ACEIs have shown that their use was associated with a reduction in the development of diabetes. Many clinical studies have documented that treatment with ACEIs or angiotensin receptor blockers decreased the incidence of Type 2 diabetes.

Angiotensin II receptor blockers (ARB) induce favourable changes in systemic blood pressure, renal hemodynamics, and proteinuria similar to those induced by angiotensin-converting enzyme (ACE) inhibition. ARBs reduce cardiovascular events mainly because of reduction in first hospitalization for congestive heart failure in hypertensive type 2 diabetic patients with albuminuria[7]. The studies suggest that ARB represents a beneficial treatment of hypertension and proteinuria in incipient and overt diabetic nephropathy. ARBs also have anti-diabetic and anti-atherosclerotic properties[10,11]. As a class, the ARBs have been associated with rare instances of acute liver injury that is usually self limited in duration, but varies in clinical expression, being usually hepatocellular but occasional cholestatic in nature[12]. All of these agents have been associated with a minimal rate of serum enzyme elevations during chronic therapy (0.2% to 2%) which are usually mild-to-moderate in severity, self-limited, and rarely require dose modification or discontinuation[9].

The results of some studies reflect that ARBs (Losartan and Telmisartan) when compared to ACE inhibitor (Ramipril) are more effective in terms of delaying the progression of diabetic nephropathy and also in providing renoprotection. Also, ARBs have the property of simultaneously decreasing the systolic B.P and albuminuria when compared to ACE inhibitor (Ramipril)[13]. This study is an attempt to compare effects of ACEI and ARBs on blood glucose control and hepatic toxicity caused by these drugs.

1.1 Aims and Objectives

- The present study is taken to evaluate the beneficial effects of Enalapril, an angiotensin-converting enzyme inhibitor (ACEI) and Telmisartan, angiotensin receptor blocker in decreasing glycosylated haemoglobin levels in diabetic nephropathy patients.
- To analyse and compare hepatic toxicity of ACEI and ARB.

II. Patients And Methods

2.1 Place of study: The study was conducted at Out-Patient and In-Patient Department of Nephrology, Osmania General Hospital, Hyderabad.

2.2 Study design: Open label and parallel group prospective randomized comparative clinical study between Enalapril and Telmisartan in diabetic nephropathy patients.

2.3 Selection criteria of the patient

Inclusion Criteria

1. Adults Patients of age group 18 - 65yrs.
2. Both males and females are included.
3. Diabetic patients.
4. Hypertensive patients.
5. Patients with urinary albumin >30mg of in a 24-hour collection.
6. Patients who are able to provide written informed consent in accordance with the Good Clinical Practice (GCP).

Exclusion Criteria

1. Pregnant patients and breast feeding mothers.
2. Severe hypertension.
3. Patients with cerebrovascular disease.
4. Patients with ischaemic heart disease, congestive cardiac failure, cardiac arrhythmia.
5. Patients with liver impairment, malignancy, diabetes mellitus.
6. Patients on other medication (hypolipidaemics, antacids, non-steroidal anti-inflammatory drugs, systemic corticosteroids).
7. Patients on multidrug antihypertensive therapy.
8. Patients who did not give written informed consent.
9. Patients showing allergic reactions to drugs in study.
10. History of angioedema during administration of ARB/ACEI.
11. Markedly poor bile secretion.
12. Patients in renal failure.

III. Methodology

Approval from Institutional Ethics Committee of Osmania Medical College, Hyderabad was obtained. After selection of patients based on the above criteria, patient was explained about the study in their own understandable language and written informed consent was obtained. After initial screening, the demographic data, medical history, findings of physical examination and clinical examination were recorded in the case report form.

3.1 Treatment

Group A patients received Tab. Enalapril 5mg orally once a day daily for 3 months.
Group B patients received Tab.Telmisartan 40mg orally once a day daily for 3 months.

3.2 Follow-up

Follow-up was done at 3 months of treatment.

HbA1C(%), LFT including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP) & bilirubin were obtained according to standard clinical laboratory methods at 0 & 3 months of treatment.
Any adverse effects of the treatment were also recorded.

3.3 HbA1C was estimated with Ion exchange resin method.

3.4 Liver function tests:

Serum bilirubin was estimated with Diazo method, end point.
SGPT (ALT) was estimated with IFCC Method.
SGOT (AST) was estimated with IFCC Method.
Alkaline phosphatase was estimated with Tris Carbonate buffer, kinetic method.

3.5 FBS/PLBS was calculated using GOD-POD (Glucose oxidase peroxidase method)
3.6 Serum creatinine was estimated by Jaffe‟s kinetic assay.
3.7 Urinary albumin was estimated by Bromo cresyl green (BCG) method.
3.8 Serum potassium was estimated by ion selective electrode method (ISE).
3.9 Compliance: The patients were called for review with filled and empty blisters of the tablets. Compliance to study medicines is measured by pill count during each follow up.

3.8 Statistical Analysis

Results were analysed using GraphPad Prism 7.0 h software for Mac Book Pro. Paired t-test to compare within the group and unpaired t-test for intergroup analysis was used, with level of significance 0.05.

IV. Observations And Results

Table 1: Age and sex distribution of patients in Group A and Group B

Parameter	Group A	Group B
Number of patients	50	50
Mean age (years)		
Males	53.7	52.3
Females	55.8	53.9
Gender		
Males	34	33
Females	16	17

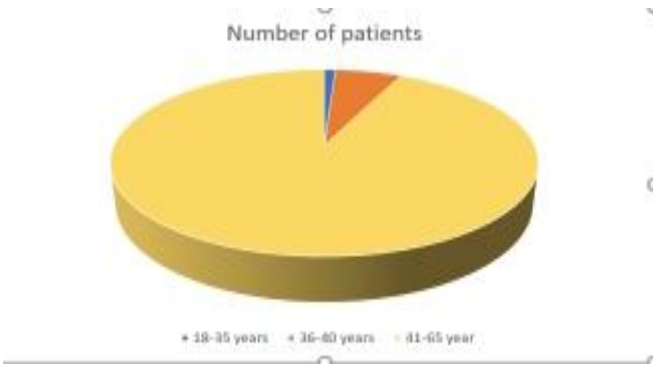

Figure 1: Age distribution of patients in Group A and Group B

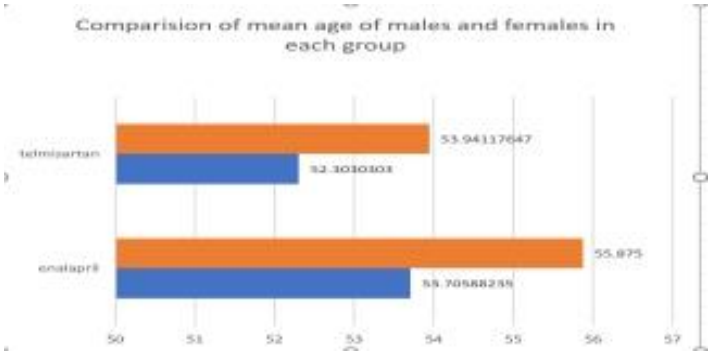

Figure 2: shows bar chart of Mean of age of patients in Group A and Group B.

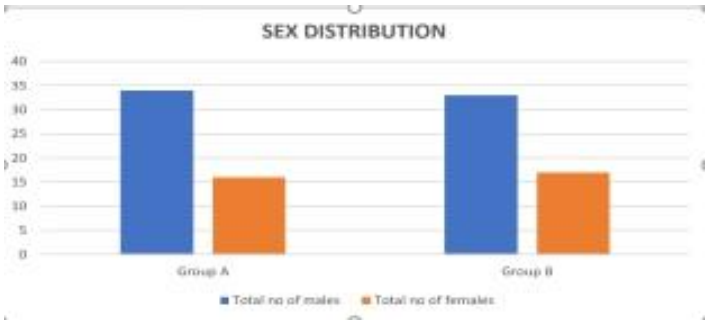

Figure 3: Sex distribution of patients in Group A and Group B

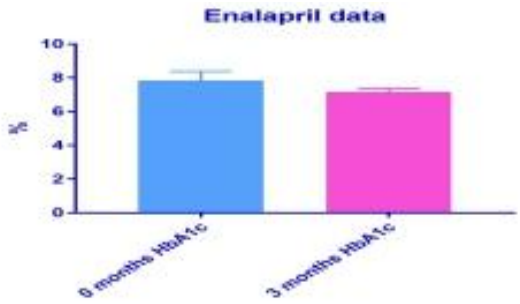

Figure 4: Effects of Enalapril on HbA1C (MEAN ± SD)

Table 2: Effects of Enalapril on FBS/PLBS, Haemoglobin values, serum creatinine, GFR and serum potassium.

PARAMETER	**BASELINE (MEAN ± SD)**	**3 MONTHS (MEAN ± SD)**
FBS	142.6 ± 1.712	128.6 ± 1.321
p value compared with baseline	<0.0001	
PLBS	191.6 ± 1.959	166.8 ± 1.579
p value compared with baseline	<0.0001	
Haemoglobin	11.89 ± 0.2474	11.5 ± 0.3672
p value compared with baseline	0.2914	
Serum creatinine	2.778 ± 0.2547	2.432 ± 0.2579
p value compared with baseline	<0.0001	
GFR	36.9 ± 1.395	39.54 ± 1.78
p value compared with baseline	0.0015	
Serum POTASSIUM	4.867 ± 0.132	5.27 ± 0.1266
p value compared with baseline	<0.0001	

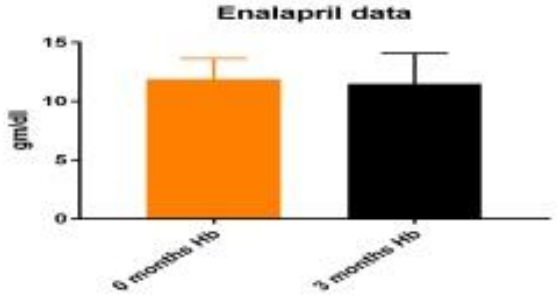

Figure 5: Effect of Enalapril on Haemoglobin (MEAN ± SD)

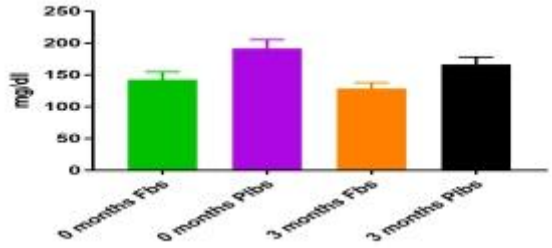

Figure 6: Effect of Enalapril on FBS & PLBS (MEAN ± SD)

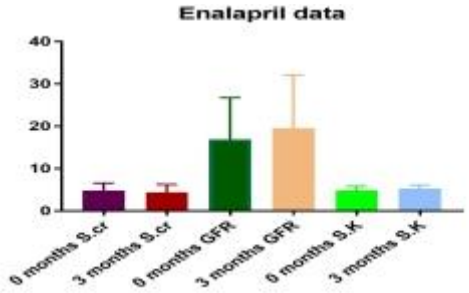

Figure 7: Effect of Enalapril on renal parameters (MEAN ± SD)

Table 3: Effects of Enalapril on LIVER FUNCTION TESTS (MEAN ±SD)

PARAMETER	BASELINE	3 MONTHS
S. BILIRUBIN	0.988 ± 0.07925	1.984 ± 0.3774
p value compared with baseline	0.0078	
ALT	18.32 ± 1.039	20.84 ± 1.043
p value compared with baseline	<0.0001	
AST	20.98 ± 0.9829	23.88 ± 1.008
p value compared with baseline	<0.0001	
ALP	73.14 ± 3.352	86.29 ± 3.071
p value compared with baseline	<0.0001	

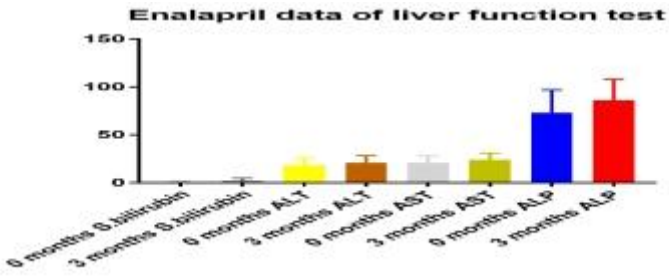

Figure 8: Effect of Enalapril on liver function tests.

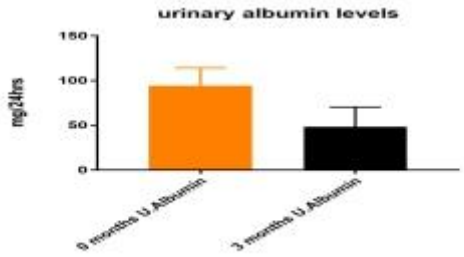

Figure 9: Effect of Enalapril on urinary albumin

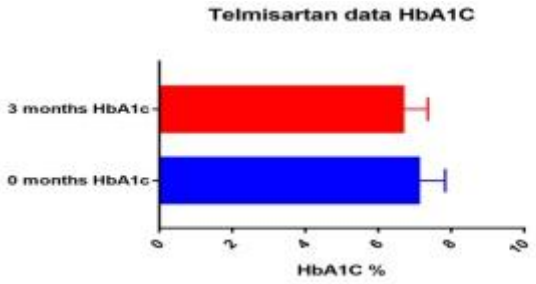

Figure 10: Effect of Telmisartan on HbA1c

Table 4: Effects of Telmisartan on FBS/PLBS, Haemoglobin values, serum creatinine, GFR and serum potassium

PARAMETER	**BASELINE (MEAN ± SD)**	**3 MONTHS (MEAN ± SD)**
FBS	141.4 ± 1.088	136.3 ± 1.109
p value compared with baseline	<0.0001	
PLBS	183.6 ± 1.462	179.1 ± 1.334
p value compared with baseline	0.0008	
Haemoglobin	12.03 ± 0.2212	12.06 ± 0.2417
p value compared with baseline	0.7687	
Serum creatinine	2.6 ± 0.2694	2.468 ± 0.2702
p value compared with baseline	<0.0001	
GFR	34.12 ± 1.177	34.76 ± 1.284
p value compared with baseline	<0.0001	
Serum POTASSIUM	5.32 ± 0.1013	5.98 ± 0.08452
p value compared with baseline	<0.0001	

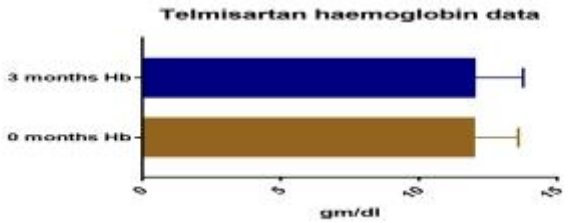

Figure 11: Effect of Telmisartan on Haemoglobin

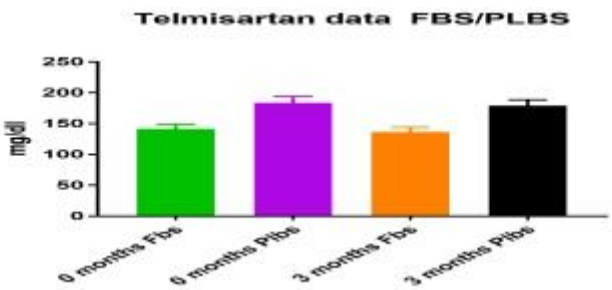

Figure 12: Effect of Telmisartan on FBS & PLBS

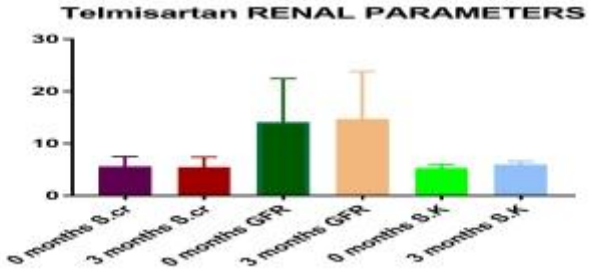

Figure 13: Effect of Telmisartan on renal parameters

Table 5: Effects of Telmisartan on LIVER FUNCTION TESTS (MEAN ±SD)

PARAMETER	BASELINE	3 MONTHS
S. BILIRUBIN	0.944 ± 0.08147	1.456 ± 0.09702
p value compared with baseline	<0.0001	
ALT	17.94 ± 1.179	20.3 ± 1.275
p value compared with baseline	<0.0001	
AST	19.74 ± 1.22	22.6 ± 1.22
p value compared with baseline	<0.0001	
ALP	70.25 ± 2.961	78.74 ± 2.762
p value compared with baseline	<0.0001	

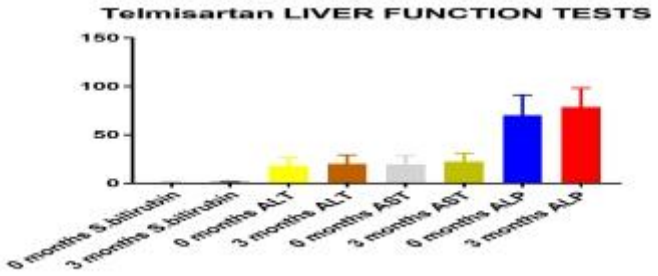

Figure 14: Effect of Telmisartan on liver function tests.

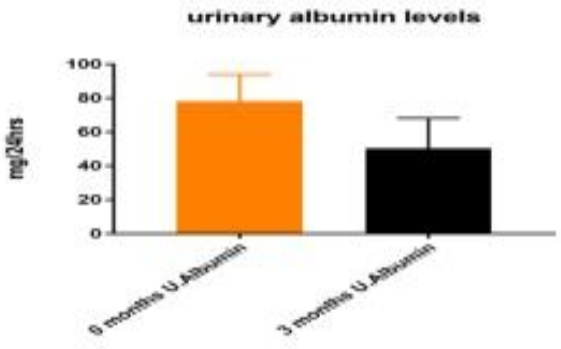

Figure 15: Effect of Telmisartan on urinary albumin.

Table 6: Comparision of effect of Enalapril and Telmisartan on HbA1C

PARAMETERS	**ENALAPRIL**	**TELMISARTAN**
HbA1C	7.166 ± 0.0275	6.716 ± 0.09059
p value comparing two groups	<0.0001	

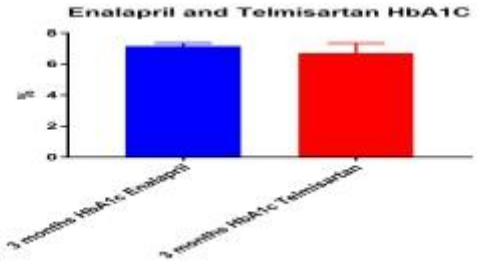

Figure 16: Comparision of effect of Enalapril and Telmisartan on HbA1C

Table 7: Comparision of effect of Enalapril and Telmisartan on Liver Function Tests

PARAMETER	ENALAPRIL	TELMISARTAN
S. BILIRUBIN	1.984 ± 0.3774, n=50	1.456 ± 0.09702
p value	0.1786	
ALT	20.84 ± 1.043, n=49	20.3 ± 1.275
p value	0.7421	
AST	23.88 ± 1.008, n=50	22.6 ± 1.22
p value	0.4212	
ALP	86.29 ± 3.071, n=50	78.74 ± 2.762
p value	0.0705	

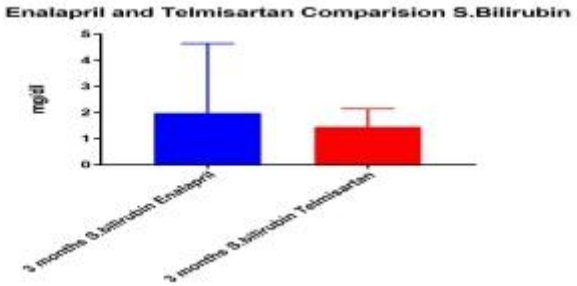

Figure 17: Comparision of effect of Enalapril and Telmisartan on S. Bilirubin

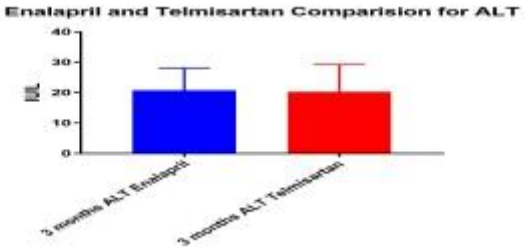

Figure 18: Comparision of effect of Enalapril and Telmisartan on ALT

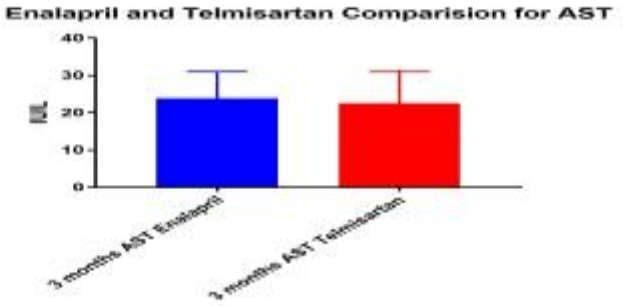

Figure 19: Comparision of effect of Enalapril and Telmisartan on AST

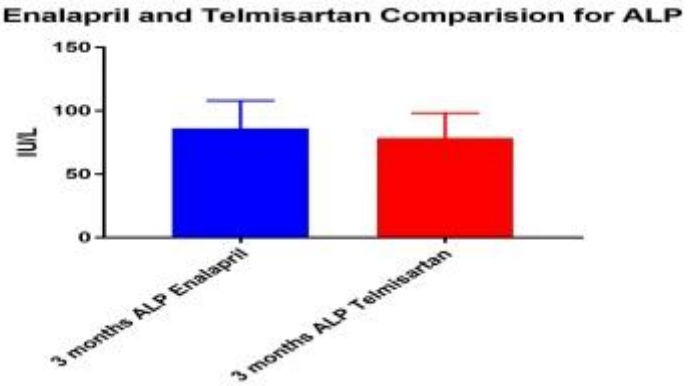

Figure 20: Comparision of effect of Enalapril and Telmisartan on ALP

Table 8: Comparision of effect of Enalapril and Telmisartan on Urinary Albumin

PARAMETERS	ENALAPRIL	TELMISARTAN
URINARY ALBUMIN	48.31 ± 3.141	50.46 ± 2.503
p value	0.5926	

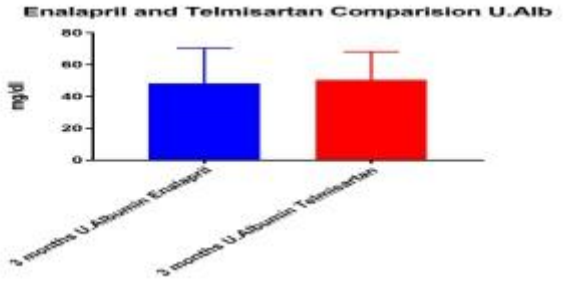

Figure 21: Comparision of Enalapril and Telmisartan on Urinary Albumin

Table 9: Loss to follow-up, compliance and total adverse effects in both Groups.

Parameter	Group A	Group B
Loss to follow-up (number)	3	2
Compliance (%)	94	96
Total adverse effects (number)	22	8

Table 10: Adverse effects in each group

Adverse effect	Group A	Group B
Dry cough	12	3
Angioedema	0	0
Headache	5	4
Hypotension	0	0
Acute renal failure	0	0

V. Discussion

Once-daily administration of Enalapril (5mg) for 1-12 weeks decreased the HbA1C significantly from 7.85 ± 0.54 to 7.17± 0.19, with p value <0.05. In this study, HbA1c, a useful measure of the efficacy of glucose-lowering treatment, had been significantly decreased in diabetic nephropathy patients receiving Enalapril. Physical activity, weight loss, and some glucose-lowering agents reduce the incidence of diabetes in people with elevated glucose levels that are just below the diagnostic threshold for diabetes. Several trials involving people with hypertension or cardiovascular disease have suggested that any agents that block or inhibit the RAS may also prevent diabetes[14].

Recent clinical trials suggest that blockade of the RAS, either by inhibiting the ACE, or by blocking the angiotensin Type 1 (AT1) receptor, may substantially lower the risk for Type 2 diabetes. **Sathiya Vinotha A. T, Ranjani R**[15] conducted a study to assess role of enalapril on oxidative stress in newly diagnosed type 2 diabetes mellitus and its correlation with glycaemic status which showed that newly diagnosed type 2 diabetics treated for 12 weeks with Enalapril and Metformin had significantly, reduced free radicals when compared with Metformin group and it goes positively with FBS and HbA1c. HbA1c decreased to 5.26±0.34 in Enalapril plus metformin group compared to 5.79±0.41 in metformin alone group.

One study in Netherland, **Adarkwah CC et al**[16] stated that for patients with type 2 diabetes, treatment with an ACE inhibitor prevented the occurrence or progression of diabetic kidney disease and is highly cost-effective if we start as early after diagnosis.

The Captopril Prevention Project (CAPPP)[17] was a prospective, randomised, open trial with blinded evaluation. Patients (n = 10985) aged 25-66 years with a measured diastolic blood pressure of 100 mmHg or more. The incidence of T2DM was lower in the captopril group than in the conventional group (odds ratio or OR: 0.86 (95% CI, 0.74-0.99); p = 0.039).

Several randomised clinical trials (RCTs) suggested that the inhibition of the renin-angiotensin system (RAS) reduces the risk of new type 2 diabetes mellitus (T2DM) in patients with arterial hypertension or with congestive heart failure. A meta-analysis of 10 RCTs including a total of 69950 non-diabetic subjects with arterial hypertension and a total of 5727 non-diabetic patients with congestive heart failure demonstrated a 22% relative risk reduction after a mean follow up of 4-5 years when using an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor AT1 blocker (ARB) as compared to placebo or various reference drugs (beta-blockers or diuretics or amlodipine). The beneficial effect was similar with ACEIs and with ARBs as well as in patients with hypertension and in those with heart failure[18].

Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study[19], to evaluate whether Ramipril reduces the risk of diabetes in people who have impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance was done in 2003, which showed that participants receiving Ramipril had normal fasting glucose levels and glucose tolerance than those receiving placebo, and the distribution of the glucose levels had shifted downward in the Ramipril group by the end of the study.

The Heart Outcomes Prevention Evaluation (HOPE) study[20] showed that, in a population at high risk for cardiovascular events, the use of Ramipril reduced cardiovascular events by 22% and diabetes by 34%, as compared with placebo.

In Telmisartan group, MEAN ± SD value of HbA1C at baseline was 7.144 ± 0.09769 and 6.716 ± 0.09059 after 3 months of treatment. p value <0.0001 which is less than 0.05, hence significant. Telmisartan has been reported to increase insulin sensitivity by acting as a partial PPAR-gamma agonist, regardless of its renin angiotensin system inhibition.

Okan Bakıner et al[21] studied the Effects of Telmisartan and Losartan on Insulin Sensitivity which showed at the beginning of the study, in both groups, starting FBS levels did not differ statistically (p=0.49). HbA1c levels were significantly lower in TELMISARTAN group (p=0.032). At the end of the study, in both groups, mean FBS and HbA1c levels did not differ significantly compared to the initial measurements.

In this study Enalapril group showed, MEAN ± SD value of HbA1C 7.166 ± 0.0275 after 3months and Telmisartan group showed 6.716 ± 0.09059, with p value <0.0001 comparing 2 groups which is less than 0.05. it indicates Telmisartan group showed more decrease in HbA1C after treatment.

Suresh Thota, **Snehapriya Voorugonda et al**[22] conducted a study of Comparison of Efficacy of Telmisartan and Enalapril in Patients with Diabetic Nephropathy, which showed HbA1C (%) value in telmisartan group 7.39 ± 1.34 and 7.56 ± 1.31 in enalapril group. According to a meta-analysis of eight trials, telmisartan was superior to other ARBs in reducing fasting plasma glucose and increasing adiponectin levels. Using an 80-mg dose, telmisartan may also reduce fasting plasma insulin levels as well as homeostasis model assessment of insulin resistance (HOMA-IR)[23].

In this study Head- to- head comparison of renal outcomes with 2 diabetes the use of an angiotensin II-receptor blocker (Telmisartan) and an ACE inhibitor (Enalapril) in subjects with type 2 diabetes and nephropathy was carried out, we determined that Telmisartan was not inferior than Enalapril in preventing the progression of renal dysfunction, measured as the decline in the urine albumin. A decline in the urine albumin is a key determinant of diabetic nephropathy. Urinary albumin value of enalapril group was 48.31 ± 3.141 and of Telmisartan group was 50.46 ± 2.503 after treatment with a p value of 0.5926 comparing both groups.

One clinical study that has directly compared the effect of angiotensin II- receptor blocker (losartan) with that of an ACE inhibitor (Enalapril) in subjects with type 2 diabetes and early nephropathy[24]. Geometric means for urinary albumin excretion (UAE) decreased significantly (P < 0.001) in patients treated with losartan from 64.1 to 41.5 μg/min and in those treated with enalapril from 73.9 to 33.5 μg/min after 52 weeks of therapy. Results indicate that a one-year course of antihypertensive therapy with either losartan or enalapril significantly reduces UAE in hypertensive type 2 diabetic patients with early nephropathy. The reduction in UAE with each treatment is similarly related to decrements in Ambulatory blood pressure. In addition, the rate of decline in GFR is similar in both treatment groups.

Suresh Thota, Snehapriya Voorugonda et al[21], conducted a study in which at the end the reduction in urine albumin was more with Enalapril (Mean difference 43.75 ± risk. 4.003) when compared with Telmisartan (Mean difference 36.49 ± 3.23). The p values were < 0.05 for both groups and it was found that reduction of diabetic nephropathy in Enalapril treatment group at the end of the study statistically differs than the Telmisartan treatment group.

In present study serum bilirubin value in both groups increased compared to baseline but it is significantly raised only in Telmisartan group. Enalapril baseline value was 0.988 ± 0.07925 and after 3months it showed a mean±sd of 1.984 ± 0.3774, with a p value of 0.0078 which is statistically insignificant. Telmisartan group had a baseline of 0.944 ± 0.081 and after treatment it showed 1.456 ± 0.09702, with a p value <0.05 which is statistically significant. ALT was raised in both groups compared to baseline and is statistically significant in both groups with p value <0.05. AST increased compared to baseline in both groups with significant p value. Alkaline phosphatase also raised in both groups.

Hepatotoxicity, usually cholestatic in nature, has been reported with captopril, enalapril, and lisinopril use. Apparent cross-reactivity has been reported twice. Potential mechanisms of injury include idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of kininase II and subsequent increased hepatic bradykinin activity. ACEIs are prescribed for many cardiovascular and renal diseases, adverse hepatic events especially cholestasis have rarely been reported with captopril, lisinopril, and fosinopril. In this study, enalapril and Telmisartan significantly elevated the liver function parameters (TSB, ALT, AST, and ALP), prolonged cholestatic hepatitis, and biliary cirrhosis may result from the use of these drugs. Monitoring of liver enzymes is advisable for patients starting on Enalapril and Telmisartan[25]. Cross-reactivity between enalapril and captopril are documented. Therefore, in patients who developed hepatotoxicity while taking one ACEI, other agents in this class should be avoided[26].

Comparing between the groups Enalapril and Telmisartan, liver function tests are not statistically different. Certain prostaglandins, such as 16, 16-dimethyl prostaglandin E, decrease bile flow rates in humans. In individuals with unusual variations in hepatic prostaglandin metabolism, exposure to ACEIs may lead to increased production of specific prostaglandins that favor bile stasis. Bile stasis may then increase leukotriene levels, with resulting hepatocellular and biliary tract toxicity, as seen in animal models of bile duct ligation.

The study undertaken in 135 hypertensive patients in Shri Ram Murti Institute of Medical Sciences, Uttar prdesh showed administration of ramipril for 2 months produced statistically significant ($p<0.05$) elevation in total serum bilirubin (TSB), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum alkaline phosphatase (ALP) concentrations of hypertensive patients.

VI. Conclusion

Telmisartan is more efficacious in glycaemic control in Diabetic nephropathy patients than Enalapril. Both drugs have similar effects of urine albumin excretion which indicates renal protection. Telmisartan and Enalapril both are equally hepatotoxic. Telmisartan has less adverse effects compared to enalapril.

6.1 Strengths of the present study:

- The present study included the age group of 18 to 65 years which is considered to be the potential target of diabetic nephropathy.
- The present study excluded diabetic nephropathy patients on multidrug antihypertensive therapy, so that the effect of the study drugs can be seen without any interactions with other anti-hypertensive drugs.
- The present study has been done for three months which provides sufficient time to evaluate the effects on HbA1c, LFT, GFR & Urinary albumin & side effects. It helped to compare the drugs, unlike the previous studies mentioned, which were conducted for a shorter period.

6.2 Limitations of the study:

- As the study was done with small sample size, the inference of the study has limited value.
- Though dose ranges are high for studied drugs i.e., 20mg-80mg for Telmisartan, 2.5-20mg for Enalapril maleate, we offered fixed dose i.e., 40mg of Telmisartan and 5mg of enalapril maleate to the studied patients.
- Follow up was planned at the end of 3 months in the study. But 5 patients didn't turn up at 3 months.
- Duration of study: A long term follow up for one year, will show the long term benefits and side effects of the drugs.

6.3 Recommendations of further work:

- Study should be carried out with bigger sample size for the results to be more accurate.
- Studies should be carried out for longer duration (for 1 year) to evaluate the long term safety and efficacy of the drugs.

References

[1]. Danaei G et al (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participa0nts. Lancet 378(9785):31–40

[2]. Xu Y et al (2013) Prevalence and control of diabetes in Chinese adults. JAMA 310(9):948–959

[3]. Roglic G et al (2005) The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care 28(9):2130–2135
[4]. Dronavalli S, Duka I, Bakris GL (2008) The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab 4(8):444–452
[5]. Dan L. Longo, Dennis L. Kasper. Harrison's Principles of Internal medicine 18th edition. Mc Graw Hill;2012;
[6]. Ferrannini E, Seghieri G, Muscelli E. Insulin and the renin-angiotensin-aldosterone system: influence of ACE inhibition. Journal of Cardiovascular Pharmacology, 1994, 24 (Suppl 3), S61-9.
[7]. Laurence L. Brunton . Goodman & Gilman's The pharmacological basis of therapeutics. 12th edition. Mc Graw Hill;2011;
[8]. Dharmendar Gupta et al. Effect of Ramipril on glycosylated haemoglobin and liver function test in patients of diabetic nephropathy. Indian journal of basic and clinical pharmacology. 2015;4(2):312-316
[9]. http://livertox.nih.gov/AngiotensinIIReceptorAntagonists.htm
[10]. Kutz TW and Pravenec M: Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the rennin-angiotensin system. Journal of Hypertension 22: 2253-2261, 2004.
[11]. Fogari R and Zoppi A. Antihypertensive drugs and fibrinolytic function. American Journal of Hypertension 19: 1293-1299, 2006
[12]. De Marzio DH, Navarro VJ. Antihypertensives. Hepatotoxicity of cardiovascular and antidiabetic medications. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 522-6. (Review of hepatotoxicity of antihypertensive agents, mentions that cases of hepatotoxicity of candesartan, irbesartan, losartan and valsartan have been published, but none were fatal and were variable in both latency to onset [1 week to 6 months] and clinical presentation [cholestatic and hepatocellular]).
[13]. Jahnavi V. Pathak, Ervilla E. Dass. A retrospective study of the effects of angiotensin receptor blockers and angiotensin converting enzyme inhibitors in diabetic nephropathy. Indian journal of pharmacology 2015; 47(2):148-152
[14]. Padwal R, Majumdar SR, Johnson JA, Varney J, McAlister FA. A systematic review of drug therapy to delay or prevent type 2 diabetes. Diabetes Care. 2005;28(3):736-44.
[15]. Sathiya Vinotha A. T.1*, Ranjani R,A prospective randomized study: role of enalapril on oxidative stress in newly diagnosed type 2 diabetes mellitus and its correlation with glycaemic status, International Journal of Basic & Clinical Pharmacology, 2017 ,6 (4), 874
[16]. Adarkwah CC, Gandjour A, Akkerman M, Silvia M. Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands-a markov model. Plos one. 2011;6(10):e26139.
[17]. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. Meta-analysis of randomised clinical trials. Diabètes & Métabolism, 2004, 30, 487-96
[18]. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the renin-angiotensin system. Drugs, 2004, 64, 2537-65
[19]. The DREAM Trial Investigators. Effect of Ramipril on the Incidence of Diabetes, New England journal of Medicine 2006; 355:1551-1562
[20]. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. JAMA 2001;286:1882-5
[21]. Okan Bakıner, Emre Bozkırlı, Eda Ertorer, The Effects of Telmisartan and Losartan on Insulin Sensitivity, Turkish Journal of Endocrinology and Metabolism, 2013; 17: 91-97
[22]. Suresh Thota, Snehapriya Voorugonda, Rajendra Prasad Adimula, Siva Subrahmanyam Bandaru, Sharvana Bhava Bandaru Sheshagiri and Venkateshwarlu Eggadi, Comparison of Efficacy of Telmisartan and Enalapril in Patients with Diabetic Nephropathy, World Journal of Medical Sciences, 2017, 14 (3): 57-61
[23]. Suksomboon N, et al. Systematic review of the effect of telmisartan on insulin sensitivity in hypertensive patients with insulin resistance or diabetes. J Clin Pharm Ther. 2012;37(3):319–27.
[24]. André Bélanger, Chantal Godin, Jean-Pierre Hallé, Stuart Ross, Noël Wright, Jean Marion, Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy, Kidney Int., 58: 762-9.
[25]. Good CB, McDermott L, McCloskey B. Diet and serum potassium in patients on ACE inhibitors. JAMA. 1995;274(7):538.
[26]. Ray K, Dorman S, Watson R. Severe hyperkalaemia due to the concomitant use of salt substitutes and ACE inhibitors in hypertension: a potentially life threatening interaction. J Hum Hypertens. 1999;13(10):717-20.

Dr Swetha G. "Comparative Study of Effect of Enalapril and Telmisartan on Glycosylated Haemoglobin and Liver Function Test in Patients of Diabetic Nephropathy." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 9, 2019, pp 52-63.