DOI: 10.14260/jemds/2015/1929

ORIGINAL ARTICLE

EFFECT OF ADDITION OF LOSARTAN TO METFORMIN ALONE AND IN COMBINATION WITH GLIMEPIRIDE OR REPAGLINIDE IN TYPE 2 DIABETES PATIENTS WITH PROTEINURIA

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HOW TO CITE THIS ARTICLE:
Momin M. A. Mujeeb, Sujit A. Divhare. "Effect of Addition of Losartan to Metformin alone and in Combination with Glimepiride or Repaglinide in type 2 Diabetes Patients with Proteinuria". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 77, September 24; Page: 13470-13483,
DOI: 10.14260/jemds/2015/1929

ABSTRACT: Diabetes mellitus is associated with increased oxidative stress due to hyperglycemia. This increased oxidative stress gives rise to micro and macro vascular complications. **MATERIALS & METHODS:** Randomized comparative prospective trial. Three groups were formed comprising of metformin + losartan, Metformin + Glimepiride + Losartan and metformin + Repaglinide + Losartan. The parameters like glycemic control, lipid profile, antioxidant status and progression of diabetic nephropthy before and after therapy was assessed by fasting blood sugar, glycated Hb, lipid profile, antioxidant status, renal function tests and proteinuria. From the group I & II comparisons our finding is that adding glimepiride or repaglinide to the basic regime of M + losartan has increased advantage and favorable effect. From comparison of group II & III finding is that repaglinide addition to the basic regime of M+ losartan had more favorable and increased advantage over glimepiride addition. The test for significant proteinuria and renal function tests was performed before enrollment and after completion of the study. After completion of the study no any patient was having significant proteinuria and all the patients have normal renal function tests. **CONCLUSION:** Losartan efficiently reduces proteinuria with adequate tolerance in presence of adequate glycaemic control. M + repaglinide + losartan combination is highly effective in controlling proteinuria. Several mechanisms may explain these effects. Although no glomerular hemodynamic parameters were analyzed in the present study, we consider that the attenuation of proteinuria reflects an improvement in the glomerular function. Losartan has been shown to reduce proteinuria by improving glomerular basement membrane characteristics. Losartan by targeting renin angiotensin aldosterone system improves overall glomerular function. This study is of interest since hypertension, which increases intra glomerular pressure and cause further progression of nephropathy, was similarly reduced with losartan administration.

KEYWORDS: Type 2 diabetes, Renal failure, Losartan, Metformin.

INTRODUCTION: What is already known to this Topic: Diabetic nephropathy and dyslipidemia are common complication of long standing diabetes.

What this Study Adds:

- The beneficial effects of glimepiride and repaglinide on lipid profile parameters may be due to improved glycaemic control and improved hemodynamic status.
- Adequate glycaemic control with metformin + glimepiride/repaglinide and losartan decreases the progression of diabetic nephropathy and cardiovascular risk in type 2 diabetes patients.

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- Losartan efficiently reduces proteinuria with adequate tolerance in presence of adequate glycaemic control. M+repaglinide + losartan combination is highly effective in controlling proteinuria

Type 2 diabetes shares several risk factors in common with coronary artery disease such as age, hypertension, dyslipidemia, obesity, physical inactivity, stress.[1] Therefore increase in prevalence of diabetes indirectly implicates an escalating risk of CAD as well. Diabetic subjects are known to have a two to four times higher risk of getting CAD.[2,3]

Diabetes mellitus is associated with increased oxidative stress due to hyperglycemia.[4] This increased oxidative stress gives rise to micro and macro vascular complications. Long term complications involves almost all vital organs like heart, eyes, kidney, blood vessels and nervous system.[5,6] These complications will lead to the development of obesity, hypertension, dyslipidemia and insulin resistance.[7,8] There is close association between complications of diabetes and diabetic dyslipidemia.[9,10] Atherosclerosis is a primary cause of death in patients with diabetes.[11,12] The pathophysiology of development of atherosclerosis is complex and multifactorial.[13,14] Diabetic dyslipidemia accounts for around 80% diabetic death due to cadiovascular complications. There is growing body of evidence to show that hyperglycemia and dyslipidemia are connected with excess of cardiovascular risk.[15,16]

The association between CAD and diabetes is strong despite the fact that there are wide ethnic and geographic variation in their prevalence. The protective female gender effect is lost in diabetic subjects, and indeed women with diabetes are possibly more prone to develop CAD than men with diabetes.Since 1990, CAD has been the leading cause of death worldwide, and this trend is expected to continue until 2020. Cardiovascular diseases accounted for 30.9% of all deaths in 1998 and 10.3% of disability adjusted life year loss. By 2020, 85% of global cardiovascular disease burden is expected to be borne by developing nations, and the increase in CAD mortality in developing nations is projected to be 120% in women and 137% in men. Thus developing nations would contribute to more than 75% of the global diabetes burden by the year 2025.[17]Currently holding 15th place in the list of causes of death worldwide, diabetes is expected to affect 300 million people worldwide by 2025.[18]

As type 2 diabetes is progressive, the repeated appraisal of glycemic control is imperative at all stages. The American Association of Clinical Endocrinologists and American college of Endocrinology advise that monotherapy is effective only when HbA1c levels 7.6% to 8.5% and then progressing to dual and triple therapy. Antidiabetic drugs with different mechanism of action are likely to have the greatest efficacy.[18]Drug therapy is indicated as an adjunct to diet and exercise. Oxidative stress hyperhypocystinemia are risk factors for cardiovascular diseases. The trial was designed to assess the effects of metformin, glimepiride or repaglinide on cardiovascular disease risk factors such as oxidative stress. Total antioxidant status were determined and compared before and after therapy.

AIMS AND OBJECTIVES:

1. To study the effect of Metformin + Losartan on glycemic control, lipid profile, antioxidant status and progression of diabetic nephropthy before and after therapy by fasting blood sugar, glycated Hb, lipid profile, antioxidant status, renal function tests and proteinuria.
2. To study the effect of Metformin + Glimepiride+ Losartan on glycemic control, lipid profile, antioxidant status and progression of diabetic nephropathy before and after therapy by fasting

blood sugar, glycosylated Hb, lipid profile, antioxidant status, renal function tests and proteinuria.

3. 3.To study the effect of metformin + Repaglinide+ Losartan on glycemic control, lipid profile, antioxidant status and progression of diabetic nephropathy before and after therapy by fasting blood sugar glycosylated Hb, lipid profile, antioxidant status, renal function tests and proteinuria.
4. To compare the changes of fasting blood glucose, glycated Hb, lipid profile, antioxidant status, progression of diabetic nephropathy and proteinuria in three groups.

MATERIALS & METHODS: The study was carried out after permission of institutional ethics committee. Patients studied as per National Cholesterol Education Programme low risk desirable lipid levels are:[16]

- Total Serum Cholesterol <200mg/dl.
- Serum triglycerides <200mg/dl.
- HDL Cholesterol >75mg/dl.
- LDL Cholesterol <100 mg/dl.

Patients having lipid levels above low risk desirable level according to National Cholesterol Education Programme were studied.

Written Informed Consent: Written informed consent in local language and English was taken from each patient after explaining the full details regarding treatment.

Inclusion Criteria: Patients with type 2 diabetes with dyslipidemia (As per National Cholesterol Education Programme),[17] obesity, significant proteinuria are included. Type 2 diabetes patients with proteinuria are particularly included in the trial to assess the effect of losartan on prerenal failure condition and to study the drug effects on progression of renal failure and diabetic nephropathy.

Exclusion Criteria:

1. Patients with type 1 diabetes.
2. Patients requiring insulin for diabetic control.
3. Patients known allergic to these drugs.
4. Patients who has taken insulin in past.
5. Patients with deranged liver function tests.
6. Patients with rapidly progressive retinopathy/ neuropathy requiring insulin.
7. Patients not willing to give informed consent.
8. Pregnancy & lactation.

Study Design: Randomized comparative prospective trial. Randomization was made by using random number table.

Total Number of Patients Studied: Three hundred (n=300) patients of type-2 diabetes with dyslipidemia (deranged lipid profile according to National Cholesterol Education Programme) were studied and was followed up for 6 month.

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GROUPS:

Group-1: Metformin + Losartan.
Group-2: Metformin + Glimepiride + Losartan.
Group-3: Metformin + Repaglinide + Losartan.

Dosage Schedule:

1. Tab. Metformin 500 mg b.i.d.
2. Tab. Glimepiride 2mg o.d.
3. Tab. Repaglinide 2mg t.d.s.
4. Tab. Losartan 100 mg o.d.

Groups	Drug dosage	Duration
Group 1 (M + losartan)	Metformin 500mg b.i.d. Losatan 100 mg od	6 month
Group 2 (M + gimepiride + losartan)	Metformin 500 mg b.i.d. Glimepiride 2 mg od Losartan 100 mg od	6 month
Group 3 (M + repaglinide + losartan)	Metformin 500 mg b.i.d. Repaglinide 2mg 8hrly Losartan 100 mg od	6 month

Table 1

Investigations before Enrollment & on Completion of Treatment: Hemogram, blood pressure measurement, liver function tests, body mass index,blood sugar fasting, glycated Hb, lipid profile parameters, total antioxidant status, plasma malondialdehyde level, serum urea level (mg/dl),serum creatinine level (mg/dl),albumin excretion rate (mg/dl).

Follow Up: On weekly follow up patients are examined for blood sugar fasting, postmeal, blood pressure (Systolic and diastolic), appearance of any new symptom or sign, adverse effects, haemogram for anemia or leucopenia.

Procedure: The study protocol was approved by institutional ethics committee. According to National Cholesterol Education Programme, three hundred type-2 diabetes patients (n=300) with deranged lipid profile parameters and deranged antioxidant status were enrolled in the study. Patients were explained about the study pattern and related hazards. Informed written consent was obtained from the patient. Those included also examined by complete blood count, liver function test, kidney function test & fundoscopy. Enrolled patients were divided into three groups of hundred each according to random number table. Each patient in respective group was provided free samples throughout the study period and was asked to visit weekly diabetic clinic. For follow up and for collection of drugs. At each follow up visit, patients were assessed for glycaemic control, history pertaining to adverse effects was asked. All patients was given diet and exercise suggestions.

Collection of Blood Samples: Patients was asked to come fasting for follow up, 2ml of venous blood sample was collected in plain bulb. The collected blood samples were centrifuged by centrifuge

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machine at 10,000 r.p.m. for 10 min and serum was separated. The separated serum was analyzed for lipid profile parameters on semi auto analyzer.

Sample Analysis: Semiautoanalyser method was used. Lipid profile parameters like serum cholesterol, serum TG, HDL-C was calculated in concentration on linear mode of semiautoanalyser.

HbA1c: Glycated Hb (HbA1c) levels were determined by Abott architect c16000 system before and after therapy.

Proteinuria: Proteinuria was determined by Albumin excretion rate in urine (mg/dl) before and after therapy.

Antioxidant Status: Total antioxidant statu (TAS: combine concentration of individual antioxidants like vitamin C, vitamin E, beta carotene and thiol group) plasma malonlydialdehyde level (MDA) was determined before and after therapy. TAS is sensitive to the changes in plasma antioxidant level and degrees of oxidative stress.[67] Plasma malonyldialdehyde is a marker of lipid peroxidation and increases in oxidative stress.[13]

Table No.1 Group I

Parameter	Before therapy	After therapy
Fasting blood sugar mg/dl	169±32.16	164.62±22.49*
HbA1c %	8.25±0.55	7.92±0.59*
Total antioxidant status mmol/l	0.98±0.03	o.97±0.18*
MDA nmol/l	7.30±1.49	6.76±1.74*
Total cholesterol (mg/dl)	238.72±16.24	234.34±18.74*
LDL cholesterol (mg/dl)	181.71±15.52	172.12±18.56*
VLDLcholesterol (mg/dl)	44.68±5.34	41.41±3.86*
Triglycerides (mg/dl)	221.32±26.27	212.54±14.23*
HDLcholesterol (mg/dl)	36.42±5.34	39.41±3.56*
Serum urea (mg/dl)	38.16±3.93	29.43±2.64*
Serum creatinine (mg/dl)	2.4±0.35	1.97±0.56*
Albumin excretion rate (mg/dl)	104.67±12.43	87.45±8.23*
Effect of Addition of Losartan to Metformin		

*Statistically not significant

Table No.2 Group II

Parameter	Before therpy	After therapy	P value
Fasting blood sugar mg/dl	171±27.23	99.17±18.63	P<0.05
HbA1c (%)	8.28±0.43	6.48±0.62	P<0.05
Total antioxidant status (mmol/l)	0.94±0.04	1.30±0.23	P<0.05
MDA (nmol/l)	7.31±2.01	3.44±1.43	P<0.05
Total cholesterol (mg/dl)	242.32±11.32	200±22.04	P<0.05
LDL cholesterol (mg/dl)	176±16.21	158.62±16.43	P<0.05

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Triglycerides (mg/dl)	222±24.24	208±17.23	P<0.05
VLDLcholesterol (mg/dl)	46.32±4.86	42.56±3.41	P<0.05
HDLcholesterol (mg/dl)	36.81±1.89	42.32±4.32	P<0.05
Serum urea (mg/dl)	43.83±2.39	17.76±1.92	P<0.05
Serum creatinine (mg/dl)	2.5±0.78	0.96±0.43	P<0.05
Albumin excretion rate (mg/dl)	126.26±10.73	38.25±7.63	P<0.05
Effect of Addition of Losartan to Metformin ± Glimepiride			

*statistically significant

Table No.3 Group III

Parameter	Before therapy	After therapy	P value
Fasting blood sugar mg/dl	170±20.97	96.03±14.03*	P<0.001
HbA1c (%)	8.27±0.60	6.23±0.51*	P<0.001
Total antioxidant status (mmol/l)	0.96±0.08	1.38±0.12*	P<0.001
MDA (nmol/l)	7.28±1.98	3.21±1.26*	P<0.001
Total cholesterol (mg/dl)	240.74±58	193±23.67*	P<0.001
LDL cholesterol (mg/dl)	172.25±20.42	142.81±18.69*	P<0.001
Triglycerides (mg/dl)	226±24.46	198±16.42*	P<0.001
VLDL cholesterol (mg/dl)	48.06±3.88	40.86±3.97*	P<0.001
Albumin excretion rate (mg/dl)	126.26±10.73	38.25±7.63*	P<0.05
Albumin excretion rate (mg/dl)	109.12±11.23	21.35±6.12*	P<0.001
Effect of Addition of Losartan to Metformin ± Repaglinide			

*statistically highly significant

TABLE 4

Parameter	Group I (M±losartan)	Group II (M± Glimepiride ± losartan)	Group III (M± Repaglinide ± losartan)	P value Group I vs II	P value Group I vs III	P value Group II vs III
Fasting blood sugar (mg/dl)	104.62±22.49	99.17±18.63	96.03±14.03	P<0.001	P<0.001	P<0.001
HbA1c (%)	6.82±0.59	6.48±0.62	6.23±0.51	P<0.001	P<0.001	P<0.001
Total antioxidant status (mmol/l)	1.25±0.18	1.30±0.23	1.38±0.12	P<0.001	P<0.001	P<0.001
MDA (nmol/l)	3.76±1.74	3.44±1.43	3.21±1.26	P<0.001	P<0.001	P<0.001
Total cholesterol (mg/dl)	204.34±18.71	200±22.04	193±23.67	P<0.05	P<0.05	P<0.05
HDL cholesterol (mg/dl)	39.91±3.21	42.56±3.41	44.32±2.89	P<0.05	P<0.05	P<0.05
Serum urea (mg/dl)	29.43±2.64	17.76±1.92	15.23±1.29	P<0.05	P<0.05	P<0.05
Albumin	87.45±8.23	38.25±7.63	21.35±6.12	P<0.05	P<0.05	P<0.05

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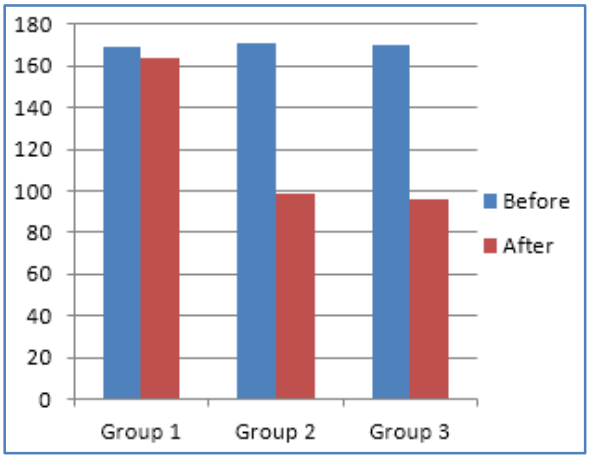
excretion rate (mg/dl)						
Serum creatinine (mg/dl)	1.97±0.56	0.96±0.43	0.93±0.26	P<0.05	P<0.05	P<0.05
Intergroup Comparison						

* P<0.05 statistically significant
** P<0.001 statistically highly significant

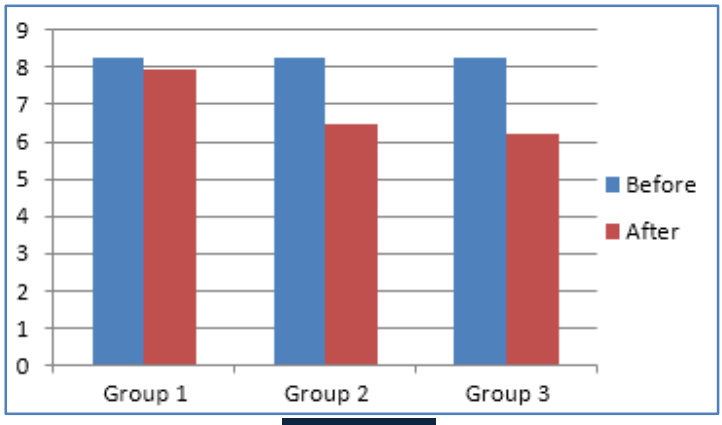
Graph 1: Comparative effect of addition of losartan to metformin alone and in combination with glimepiride or repaglinide on fasting blood sugar level.



Graph 1

Group 1 statistically not significant, Group 2 statistically significant (P<0.05), Group 3 statistically highly significant (P<0.001).

Graph 2: Comparative effect of addition of losartan to metformin alone and in combination with glimepiride or repaglinide on glycosylated Hb.



Graph 2

Group 1 statistically not significant, Group 2 statistically significant (P<0.05), Group 3 statistically highly significant (P<0.001).

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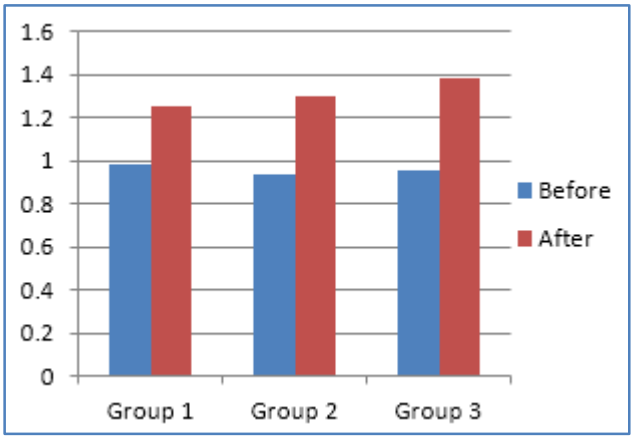
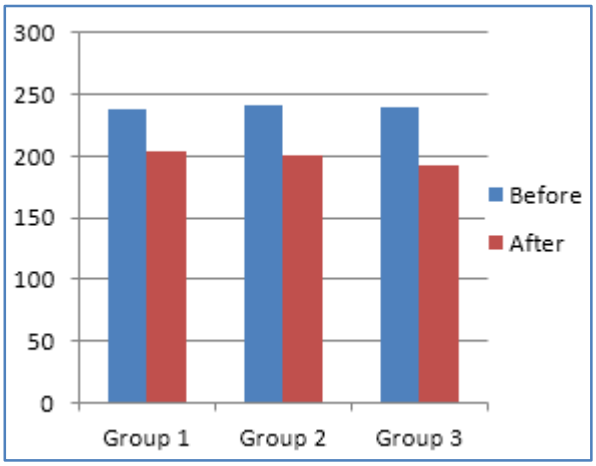
Graph 3: Comparative effect of addition of losartan to metformin alone and in combination with glimepiride or repaglinide on total antioxidant status.



Graph 3

Group 1 statistically not significant, Group 2 statistically significant (P<0.05), Group 3 statistically highly significant (P<0.001).

Graph 4: Comparative effect of addition of losartan to metformin alone and in combination with glimepiride or repaglinide on total cholesterol level.



Graph 4

Group 1 statistically not significant, Group 2 statistically significant (P<0.05), Group 3 statistically highly significant (P<0.001).

Intergroup Comparison: Thus from the group I & II comparisons our finding is that adding glimepiride or repaglinide to the basic regime of M + losartan has increased advantage and favourable effect. From comparison of group II & III finding is that repaglinide addition to the basic regime of M+ losartan had more favourable and increased advantage over glimepiride addition.

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RESULTS: Patients (n=300) of type 2 diabetes completed the study. A comparative evaluation of effect of addition of losartan to metformin alone and in combination with glimepiride or repaglinide on fasting blood sugar, glycated Hb antioxidant status, renal function tests and lipid profile was done. As shown in graph 1 fasting blood sugar level values were decreased in group I (M + losartan) from 169±32.16 to 164.62±22.49 when compared to baseline values which is statistically not significant.. In group II (M+ glimepiride+ losartan) blood sugar level values were decreased from 171±27.23 to 99.17±18.63 and this change was statistically significant (P<0.05). In group III (M+ repaglinide + losartan) blood sugar level values were decreased from 170±20.97 to 96.03±14.03 and this change was statistically highly significant(P<0.001).

As shown in graph 2 glycated Hb level values were decreased in group I (M + losartan) from 8.25±0.55 to 7.92±0.59 when compared to baseline values which is statistically not significant. In group II (M+ glimepiride+ losartan) glycated Hb level values were decreased from 8.28±0.43 to 6.48±0.62 and this change was statistically significant (P<0.05). In group III (M+ repaglinide + losartan) glycated Hb level values were decreased from 8.27±0.60 to 6.23±0.51 and this change was statistically highly significant (P<0.001).

As shown in graph 3 total antioxidant status values were increased in group I (M + losartan) from 0.98+0.03 to 1.25±0.18 when compared to baseline values which is statistically not significant. In group II (M + glimepiride + losartan) total antioxidant status values were increased from 0.94+0.04 to 1.30±0.23 and this change was statistically significant (P<0.05). In group III (M + repaglinide +losartan) total antioxidant status values were increased from 0.96±0.08 to 1.38±0.12 and this change was statistically highly significant (P<0.001).

As shown in graph 5 total cholesterol values were decreased in group I (M + losartan) from 238.72±16.24 to 204.34±18.71 when compared to baseline values and tis change was statistically not significantly. In group II (M+ glimepiride+ losartan) total cholesterol values were decreased from 242.32±11.32 to 200±22.04 and this change was statistically significant (P<0.05). In group III (M+ repaglinide + losartan) total cholesterol values were decreased from 240.74±58 to 193±23.67 and this change was statistically highly significant(P<0.001).

As shown in graph 10 serum urea level values were decreased in group I (M + losartan) from 36.42±2.34 to 39.91±3.21 when compared to baseline values (P=NS). In group II (M + glimepiride + losartan) HDL cholesterol values were decreased from 36.81±1.89 to 42.56±3.41 and this change was statistically significant (P<0.001). In group III (M + repaglinide + losartan) HDL cholesterol values were decreased from 36.72±2.29 to 44.32±2.89 and this change was statistically highly significant (P<0.001).

Renal function tests and Proteinuria: All the patients included in the study was having significant proteinuria and mild derangement of renal function tests (serum urea level, serum creatinine level) before inclusion. The test for significant proteinuria and renal function tests was performed before enrollment and after completion of the study. After completion of the study no any patient was having significant proteinuria and all the patients have normal renal function tests. It indicates that adequate glycemic control with M+glimepiride/repaglinide and losartan decreases the progression of renal failure.

Intergroup Comparison: As depicted in table 4, P value for group I (M+ losartan) versus group II (M + glimepiride + losartan) was statistically highly significant (P<0.001) for fasting blood sugar, glycated Hb, total antioxidant status and MDA levels while it was statistically significant (P< 0.05) for

lipid profile parameters showing superiority of group II over group I and added benefit of addition of glimepiride.

As depicted in table 4, P value for group I (M+ losartan) versus group III (M + repaglinide + losartan) was statistically highly significant (P<0.001) for fasting blood sugar, glycated Hb, total antioxidant status and MDA levels while it was statistically significant (P< 0.05) for lipid profile parameters showing superiority of group II over group I and added benefit of addition of repaglinide. Thus glimepiride or repaglinide to the basic regime of M+ losartan has increased advantage and favourable effect.

As depicted in table 4, P value for group II (M+ glimepiride + losartan) versus group III (M + repagliniride + losartan) was statistically highly significant (P<0.001) for fasting blood sugar, glycated Hb, total antioxidant status and MDA levels while it was statistically significant (P< 0.05) for lipid profile parameters showing superiority of group III over group II. Thus repaglinide addition to the basic regime of M+ losartan had more favourable and increased advantage over glimepiride addition.

Adveres events	Group I (n=100)	Group II (n=100)	Group III (n=100)
Nausea	3	2	4
Vomiting	4	3	5
fatigue, tiredness	2	1	2
Headache	1	1	1
Anemia	0	0	1
upper respiratory tract infection	3	2	1
major hypoglycemic episodes	0	1	2
minor hypoglycemic episodes	1	4	4
diabetic retinopathy	1	0	0
diabetic neuropathy	1	2	1
Diarrhea	3	3	2
Rash	0	1	2
Arthralgia	2	2	3
Leucopenia	1	2	3
metallic taste	2	4	3
Adverse Events			

DISCUSSION & CONCLUSION: Oxidative stress means an imbalance between the production of reactive oxygen species and the antioxidant defense system, which buffers the oxidative damage. Oxidative stress is impicated in the pathogenesis of several diseases including diabetes and atherosclerosis. Oxidative stress also impairs insulin action and has been demonstrated in type 2 diabetes, and this impairment might be due to several factors, such as membrane fluidity alterations, decreased availability of nitric oxide and increased intracellular calcium content. Serum total antioxidant status combines the concentrations of individual antioxidants, such as vitamin C and E, beta carotene and thiol groups and also their synergists. Total Antioxidant status is sensitive to the changes in plasma antioxidant levels and degrees of oxidative stress. Plasma malonyldialdehyde

(MDA) is a marker of lipid peroxidation and increases in oxidative stress states. Recent studies have documented increased oxidative stress in patients with diabetes with dyslipidemia which may increase the risk of CAD in such patients.[8]

Use of oral antidiabetic, predominantly metformin, glimepiride, repaglinide have been shown to improve insulin sensitivity. Metformin inhibits hepatic glucose production and enhances peripheral tissue sensitivity to insulin, resulting in a decrease in insulin secretion.[16]

Oxidative stress is an accepted risk factor for the development of CAD. Diabetes and dyslipidemia is associated with an increased risk of CAD.[10]

Group I results showed that metformin 500mg b.i.d. + losartan 100 mg o.d. for 6 month has no statistically significant effect on glycaemic control, antioxidant status, progression of diabetic nephropathy and does not produce statistically significantly improvement in lipid profile parameters such as reduction in total cholesterol, serum TG, LDL-C and improvement in HDL-C. These results contradicts the findings of M Browlee et al,[7] D Rodbard et al.[5]

J B Buse et al [31] reported that metformin at higher dose (1000mg t.d.s.) reduced total cholesterol and other lipids. Our negative effects of metformin may be due to low dose of metformin in the trial. (500mg b.i.d.)

The study also contradicts the findings of Ralph et al[18], A Ceriello et al.,[8] finding that metformin produced significant reduction in total cholesterol, triglycerides, LDL-C with significant increase in HDL-C.

Group II results shows that metformin 500mg b.i.d. + glimepiride 2 mg o.d. + losartan 100 mg o.d. for 6 month has shown good glycaemic control, improves antioxidant status, slows the progression of diabetic nephropathy and statistically significantly improvement in lipid profile parameters such as significant reduction in total cholesterol, serum TG, LDL-C and significant improvement in HDL-C.

These results are in accordance with studies carried out by M Jask et al,[11] Viswanathan M et al,[9] reporting that glimepiride produces significant reduction in total cholesterol and TG.

Simultaneously, the study confirms the findings of T Allavoine et al,[14] reportng that metformin + glimepiride combination produces good glycaemic control, improves antioxidant status and has favourable effect on total cholesterol, HDL-C, LDL-C but contradicts the findings with serum triglycerides.

Our findings are in accordance with K P Singh et al, [19] reporting that metformin +glimepiride combination produced good glycaemic control and halts the progression of diabetic nephropathy in patients with proteinuria.

Group III results showed that metformin 500mg b.i.d.+ repaglinide 2mg 8hourly + losartan 100 mg o.d. for 6 month has shown good glycaemic control, improves antioxidant status, slows the progression of diabetic nephropathy and statistically significantly improvement in lipid profile parameters such as significant reduction in total cholesterol, serum TG, LDL-C and significant improvement in HDL-C. These observations are statistically highly significant. These results are in accordance with studies carried out by Peter H Benett et al,[15] showing that metformin repaglinide combination has beneficial effects on blood sugar level, antioxidant status, lipid profile and on progression of diabetic nephropathy.

Our study contradicts the findings of V Sheshiah et al,[16] reporting that repaglinide alone has no effect on diabetic nephropathy and does not produce any change in tal cholesterol, TG, HDL-C, LDL-C and also with studies carried out by Richard C et al,[17,18] showing that glimepiride or repaglinide

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alone and in combination with metformin has no effect on antioxidant status, lipid profile or diabetic nephropathy. In addition the present study also for the first time tried to evaluate the effect of losartan on progression of diabetic nephropathy in an environment of good glycaemic control.

Since there is strong association with low HDL-C, elevated triglycerides and higher risk of coronary heart disease in patients with type-2 diabetes, suggesting that metformin, glimepiride and repaglinide in combination with losartan reduces cardiovascular risk and diabetic nephropathy.

Intergroup comparison has shown that the combination of metformin + repaglinide + losartan has more beneficial effects on glycaemic control, lipid profile parameters, antioxidant status and progression of diabetic nephropathy than the combination of metformin + glimepiride+ losartan. Simultaneously the intergroup comparison had shown that the combination of metformin+ glimepiride + losartan and metformin + repaglinide + losartan have more favourable beneficial effects on glycaemic control, lipid profile parameters, antioxidant status and progression of diabetic nephropathy than metformin + losartan group.

The beneficial effects of glimepiride and repaglinide on lipid profile parameters may be due to improved glycaemic control and improved hemodynamic status. Though metformin is typically the initial choice for obese patients but as monotherapy is inadequate at maintaining long term glycaemic control with approximately 40% patients requiring addition of sulfonylurea or repaglinide.[18] Therefore a more rational approach in these patients may be to combine metformin + losartan with glimepiride/repaglinide in type 2 diabetes patients with proteinuria to get increased advantage and favourable effect.

The combination of metformin + losartan do not have favorable effect on long term glycaemic control, antioxidant status and lipid profile parameters in type-2 diabetes patients with proteinuria and it is inferior to repaglinide or glimepiride. The most ideal combination would be metformin + repaglinide + losartan in type-2 diabetes patients with proteinuria, deranged lipid profile parameters and deranged antioxidant status.

Thus to conclude grading of the groups are as follows: M + losartam < M + glimepiride + losartan < M+repaglinide + losartan.

Losartan efficiently reduces proteinuria with adequate tolerance in presence of adequate glycaemic control. M+ repaglinide + losartan combination is highly effective in controlling proteinuria. Favourable data of losartan in terms of an antiproteinuric effect are consistent with Jin H M.[2] Several mechanisms may explain these efects. Although no glomerular hemodynamic parameters were analyzed in the present study, we consider that the attenuation of proteinuria reflects an improvement in the glomerular function. Losartan has been shown to reduce proteinuria by improving glomerular basement membrane characteristics. Losartan by targeting renin angiotensin aldosterone system improves overall glomerular function. This study is of interest since hypertension, which increases intraglomerular pressure and cause further progrssion of nephropathy, was similarly reduced with losartan administration.

Another possibility for the renoprotective effect of ARBs involves prevention of glomerular phenotypic modulation following glomerular injury. Glomerular phenotypic changas have been detected in 5/6 nephrectomized rats, in contrast to negligible glomerular changes in sham operated rats. However, a selective ARB, TCV 116, inhibited these changes. Glomerulosclerosis involves hyperplasia of phenotopically modified mesangial cells. Losartan may inhibit or prevent this modulation.[19]

DOI: 10.14260/jemds/2015/1929

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FINANCIAL OR OTHER COMPETING INTERESTS: None

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Date of Submission: 15/05/2014.
Date of Peer Review: 16/05/2014.
Date of Acceptance: 18/09/2015.
Date of Publishing: 24/09/2015.