# Original Article

# Effect of Atorvastatin and Losartan on Glomerular Filtration Rate in Patients With Mild to Moderate Chronic Kidney Disease

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## Abstract

***Background:*** *Atorvastatin, a member of HMG CO-A reductase inhibitors, has been shown to have renoprotective effect in patients with Chronic Kidney Disease (CKD). Statins are supposed to decrease the oxidized lipid particles, suppress the activity of inflammatory mediators and prevent vascular thrombosis and thus could minimize renal cell damage. Losartan, an antihypertensive drug also diminishes proteinuria in patients with chronic kidney diseases or diabetes mellitus. Therefore the effect of concurrent use of atorvastatin and losartan on Glomerular Filtration Rate (GFR) could be a matter of interest from both Pharmacological and Clinical perspective.* ***Objective:*** *To assess the renoprotective effect of atorvastatin and losartan in patients with chronic kidney disease treated at Bangabandhu Sheikh Mujib Medical University (BSMMU).* ***Materials and Method:*** *Total forty four (44) patients suffering from CKD (stage one to stage three) were enrolled into two groups. Patients in Group A, received atorvastatin (10 mg) and losartan (50 mg) once daily for eight weeks. Patients in Group B, received losartan but not atorvastatin for the same duration. Serum creatinine level was measured at the commencement and also after eight weeks to calculate estimated glomerular filtration rate (eGFR) in individual patients with MDRD (Modification of Diet in Renal Disease) study equation.* ***Results:*** *There was significant ($P < 0.001$) reduction of Serum Creatinine and significant ($P < 0.001$) increase in e GFR in the patients, treated with atorvastatin and losartan.* ***Conclusion:*** *Concurrent administration of atorvastatin and losartan increased glomerular filtration rate (GFR) significantly in patients with chronic kidney disease.*

**Keywords:** *Atorvastatin, Losartan, Glomerular filtration rate, Chronic kidney disease*

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## Introduction

Chronic kidney disease (CKD) has emerged as a global publichealth burden for its increasing number of patients, high risk of progression to end-stage renal disease (ESRD), and poorprognosis of morbidity and mortality.[1] In the United States for instance, more than one in every ten persons suffers from some stages of CKD.[2] In Bangladesh, the rate of prevalence seems to be higher (>15%).[3]

Hepatic Hydroxy Methyl Glutaryl Co-A (HMG Co-A) reductase inhibitorsor Statins, are a group of drugs quite effective in treating dyslipidemia. In some studies, they have shown some other effects beyond their lipid lowering effect, considered as the "pleiotropic effects"[4]. They are related to the anti- inflammatory, anti-oxidant and fibrinolytic properties of statins.[5,6] Their role in renoprtection has attracted much attention from the researchers.[7,8] Statins are believed to down regulate the production and renal infiltration of T-cells, T-helper cells, macrophages, and neutrophils, leading to reductions in renal inflammation, glomerular scarring, and mesangial proliferation.[9]

Some authors have also mentioned their effect helpful for lowering of blood pressure when used along with renin-angiotensin-aldosterone system (RAAS) inhibitors or Calcium Channel blockers (CCB)10. Their anti- oxidant effect also reduces the proportion of oxidized LDL to prevent renal damage. Renal antioxidant effect with consequent endothelial

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function regulation of renal vasculature following statin treatment may also account for pleiotropic protection against renal injury.[11]

It has been claimed that, statins consistently lower the incidence of death and major cardiovascular events by about 20% in CKD patients not requiring dialysis.[12] Observing the renal beneficial effect of statins, the Kidney Disease Improving Global Outcomes (KDIGO) lipid work group has recommended statins as lipid lowering agent for patients with chronic kidney disease.[13]

Still the beneficial effects of statins on renal outcomes are controversial and some authors have found their role doubtful.[14] So, more evidence in favor to establish such effect is needed at present.

Losartan is an antihypertensive agent of Angiotensin receptor blocker group. It is recommended for hypertensive patients with chronic kidney diseases and diabetes, as it decreases the resistance of the efferent arterioles in the glomerular capillary and thus reduces proteinuria.[15] Losartan improves renal outcomes in patients with type 2 DM and nephropathy over and above that attributable to BP control alone, which in major part is explained by its anti-albuminuric effect.[16]

But its effect on glomerular filtration rate is still controversial. Some researchers states their effect as an increase in GFR, while the others found an initial decline due to reduction of blood pressure causing decrease in filtration pressure in the glomeruli1.[7] So, it's effect on GFR alone and in combination of other drugs having impact on GFR is a matter of interest from pharmacological aspect as well as for selection of drugs for CKD patients. Because estimated glomerular filtration rate (eGFR) has become a standard method to evaluate CKD based on diagnostic criteria and classification by the National Kidney Foundation, USA.[18]

## Materials and Methods

The study was carried out in the Departments of Pharmacology and Department of Nephrology (both indoor and outdoor) at Bangabandhu Sheikh Mujib Medical University, Dhaka in between September, 2014 to January, 2016. A total 44 patients with CKD (age 25-65 years) receiving Losartan with or without Atorvastatin were enrolled for the study. Patients with CKD stage 4 or 5, having dialysis therapy or having severe hepatic, cardiovascular, infectious or systemic diseaseunrelated to CKD were excluded.

The research protocol was reviewed and approved by the Institutional Review Board of BSMMU. Written informed consents were taken from the participants.

**Estimation of serum creatinine level by alkaline picrate method**

Creatinine forms an alkaline solution as orange red coloured complex with picric acid. The absorbance of this complex is proportional to the creatinine concentration in the sample. Creatinine + picric acid Creatinine - picric acid complex The absorbance of this complex can be measured in spectrophotometer at 492 nm wavelength.

**eGFR calculation by MDRD formulla**

It can be calculated from serum creatinine level by using MDRDequation (The Modification of Diet in Renal Disease study equation) with four variables.

GFR (ml/min/1.73 $m^2$) = $175\times(S.\ Cr)^{-1.154}\times(Age)^{-0.203}\times$ (0.742, if female)

The following online calculator was used to calculate e GFR of every patient.[19]

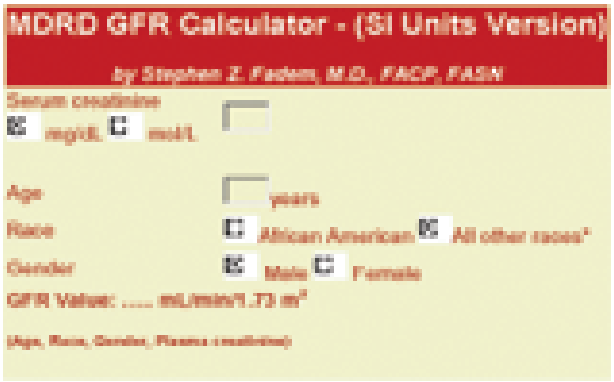


**Figure 1:** Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values

Mean values and Standard deviations (mean ± SD) were calculated for different groups. Before- after and parallel differences of different interventions were analyzed. Comparison of data was done by paired and unpaired 't' test. Calculated 'p' value suggested the level of significance (* significant at $p < 0.05$,

## Results

The results obtained following administration of atorvastatin withlosartan concurrently in CKD patient group (Group A) in contrast to those of losartan administered group (Group B) were recorded, elaborated and shown in tabulated and graphical presentation in the following paragraphs.

Prior to present the results, the demographic characteristics of the study population are presented.

**Table I:** Demographic characteristics of the study population

| Variables | Group A(n=22) | Group B(n=22) |
|---|---|---|
| Age(in years, mean±SD) | 50.95±11.9 | 46.54±12.1 |
| Male(n)% | 16(36.3%) | 15 (34.1%) |
| Female(n)% | 06 (13.6%) | 07(16%) |
| DM (n)% | 09 (20.5%) | 11(25%) |
| CGN(n)% | 08 (18.18%) | 07(16%) |
| HTN(n)% | 05(11.36%) | 04(9%) |

DM = Diabetes Mellitus induced nephropathy

CGN = Chronic Glomerulonephritis induced nephropathy
HTN = Hypertension induced nephropathy
One patient from group A and three from group B were dropped out. So, twenty one (21) patients from Group A and nineteen (19) from Group B have completed the study.

**Table II:** Baseline values of the parameters in both groups

| Variables | Group A (n=21) | Group B (n=19) | P value |
|---|---|---|---|
| Serum Creatini (mg/dl) | 1.76 ± 0.50 | 1.73±0.65 | 0.87 (> 0.05) |
| Estimated GFR (ml / min / 1.73 $m^2$ body surface area) | 46.33 ± 20.04 | 49.47 ± 24.01 | 0.65 (> 0.05) |
| Serum Total cholesterol ( mg / dl) | 227.62 ±47.12 | 226.16 ± 45.6( | 0.92 (> 0.05) |
| Reduced glutathione (mg / gm of) Hb | 0.92 ± 0.37 | 0.86 ± 0.36 | 0.607 (> 0.05 |

Values are expressed as mean±SD.
P value was calculated by unpaired t-test

Baseline serum creatinine value (mean ± SD) in Group A patientswas 1.76 ± 0.50 (mg/dl).
After eight (08) weeks of treatment with losartan and atorvastatin in Group A patients the serum creatinine value (mean ± SD) was decreased to 1.65 ± 0.48 (mg/dl) which was significantly less than the previous value in Group A patients.
On the other hand,baseline serum creatinine value (mean ± SD) in Group B was 1.73±0.65(mg/dl).
After eight (08) weeks of treatment with losartan without any lipid lowering agent in Group B patients the serum creatinine value ( mean ± SD) was decreased to 1.64 ± 0.56 ( mg/dl) which was not significantly lesser than the previous value in Group B patients.

**Table III:** Changes in serum creatinine level in both groups

| Variable | Group A (n= 21) | | P value | Group B (n=19) | | P value |
|---|---|---|---|---|---|---|
| | Before | After | | Before | After | |
| Serum Creatinine | 1.76 ± 0.5 | 1.65 ± 0.48 | 0.0003 | 1.73 ± 0.65 | 1.64 ± 0.56 | 0.0502 |

Values are expressed as mean±SD.
P values were obtained by Paired't' test within same groups.

**Serum creatinine**

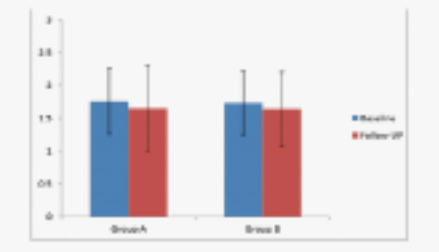

**Figure 2:** Bar diagram showing (mean ± SD) concentrations of serum creatinine (mg/dl) at baseline and after 08 weeks

Pvalue <0.001for Group A (Significant) Pvalue > 0.05 for Group B (not significant)

**Changes in e GFR level in both groups**
Baseline e GFR value (mean ± SD) in Group A patientswas 46.33 ± 20.04 (ml / min / 1.73 $m^2$ body surface area).
After eight (08) weeks of treatment with losartan and atorvastatin in Group A patients the eGFR value (mean ± SD) was increased to 49.34 ± 20.47 (ml/min/1.73 $m^2$ body surface area) which was significantly higher than the previous value in Group A patients.
On the other hand, baseline eGFR value (mean ± SD) in Group B was 49.47± 24.01 (ml / min / 1.73 m2body surface area)
After eight (08) weeks of treatment with losartan without any lipid lowering agent in Group B patients the eGFR value (mean ± SD) was increased to 50.16 ± 21.26 (ml / min / 1.73 $m^2$ body surface area) which was not significantly higher than the previous value in Group B patients.

**Table IV:** Changes in e GFR level in both groups

| Variable | Group A (n=21) | | P value | Group B (n=19) | | P value |
|---|---|---|---|---|---|---|
| | Before | After | | Before | After | |
| eGFR | 46.33 ± 20.04 | 49.34 ± 20.47 | 0.0051 | 49.47 ± 24.01 | 50.16 ± 21.26 | 0.663 |

Values are expressed as mean±SD.
P values were obtained by Paired 't' test within same groups.
e GFR = Estimated Glomerular Filtration Rate ((ml / min / 1.73 m2body surface area)
P value < 0.001= Statistically significant change in Group A
P value > 0.05= Statistically non-significant change in Group B

**eGFR**

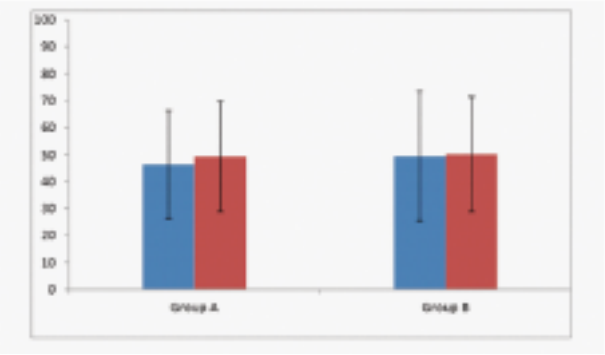

**Figure 3:** Bar diagram showing the (mean±SD) eGFR values at baseline and after 08 weeks

## Discussion

This study was designed to observe the effect of Atorvastatin and Losartan on glomerular filtration rate in CKD patients. Serum creatinine value in Group A patients decreased from 1.76 ± 0.50 to1.65 ± 0.48 (mg /dl) which was significant (P < 0.001) and in Group B from 1.73± 0.65 to 1.64± 0.56 (mg /dl) which was not significant (> 0.05). Reduction in creatinine level had lead the eGFR value in Group A patients to increase significantly (P < 0.001) from 46.33 ± 20.04 to 49.34 ± 20.47 (ml / min / 1.73 $m^2$ body surface area).

Similar increase in eGFR by virtue of treatment with atorvastatin was reported byKoseet. al. in 2014.[20] In that study eGFR was significantly increasedfrom 51.1± 7.82 mL/min/1.73 m2 to 61.8± 13.3 mL/min/1.73 m2 while no significant increase was reported with rosuvastatin treated group.

On the other hand, baseline e GFR value (mean ± SD) in Group B was 49.47± 24.01 (ml / min / 1.73 m2body surface area). After eight (08) weeks of treatment with losartan without any lipid lowering agent in Group B patients the eGFR value (mean ± SD) was changed to 50.16 ± 21.26 (ml / min / 1.73 m2 body surface area) which was not significantly higher but somehow static around the previous value in Group B patients.

Similar protective effect on eGFR by the Angiotensin receptor blockers (ARBs) was reported by Weil et.al. in 2013.[21] They had tested the efficacy of Angiotensin receptor blockers in early diabetic kidney disease. They had performed a 6-years randomized clinical trial in 169 American Indians with type 2 diabetes and normoalbuminuria (albumin/creatinine ratio [ACR] <30 mg/g; n = 91) or microalbuminuria (ACR 30-299 mg/g; n=78) at baseline. The primary outcome parameter was decline in glomerular filtration rate (GFR) to 60 mL/min or to half the baseline value in subjects who entered with GFR <120 mL/min.At the end of the study only nine subjects reached the GFR decline point, indicating the GFR protecting effect of the ARBs.Treatment with ARBs also preserved some features of kidney structure.

## Conclusion

The results obtained by the present study indicate that, concurrent administration of atorvastatin with losartan increasedestimated glomerular filtration rate (GFR) significantly. The combination could be beneficial for the patients suffering from mild to moderate chronic kidney disease (CKD).

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