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**Original Article**

# Effect of Losartan on Oxidative Stress and Lipid Profile in Patients with Essential Hypertension

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## ABSTRACT

**Background:** Biomarkers measured for systemic oxidative stress are elevated in hypertension (HTN). Many antihypertensive drugs reduces oxidative stress along with normalization of blood pressure. The present study aimed to determine the effect of losartan on oxidative stress and lipid profile in patients with essential hypertension.

**Materials & Methods:** This prospective cohort study enrolled 200 essential hypertensive treatment naïve patients. After proper consent, lorsartan 50mg was prescribe once daily to all patient. 5cc blood was extracted and divided into 2 portions in EDTA and gel tube. The lipid profile and anti-inflammatory markers including ceruloplasmin assay, total antioxidant status (TAS) and malondialdehyde (MDA) assay, glucose assay, albumin assay, urea and creatinine assay were evaluated using commercially available kits. All the patients were followed for a period of 30 days and after follow-up all the patients were re-examined, the blood pressures were recorded and all the investigation markers were repeated. The data was analyzed using SPSS version 22.0.

**Results:** In total 200 patients, 10 were lost during follow-up. In 190 hypertensive patients, 100 (52.6%) were males while 90 (47.4%) were females. The mean age was 45.35 ± 0.96 years. Statistical significant differences were observed in lipid profile markers including total cholesterol, triglycerides, LDL and VLDL with p-values <0.001. Similarly, statistical significant differences were observed in oxidative stress markers including MDA levels, TAS levels and ceruloplasmin levels with p-values <0.001. No statistical differences were observed in BMI and HDL values with p-values >0.05.

**Conclusion:** Despite good anti-hypertensive effect of losartan, this drug is also effective in reducing oxidative stress and lipid profile thus helpful in reducing complications related to hypertension.

**Key words:** Hypertension, losartan, oxidative stress, lipid profile

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## Introduction

HTN is defined as a sustained increase in SBP (systolic blood pressure) ≥140mmHg and/or DBP (Diastolic blood pressure) ≥ 90mmHg, or taking medicine for management of blood pressure. (The British HTN Society defines HTN as a BP >140/90 mmHg). [1] Hypertension (HTN) is the leading cause of cardiovascular diseases worldwide in developing as well as industrialized countries.[2] The prevalence of HTN varies with variables like age, education and race etc.[3] Estimated global prevalence in persons above 25 years of age was 40% in 2008 which equals to one billion people.

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This is predicted to go beyond 1.5 billion by the year 2025. Prevalence of this global epidemic is equally high in different countries of Asia.[4] According to Pakistan National Health Survey (PNHS), prevalence of HTN in less than 20 years old ranges from 5-10% whereas it ranges in over 60 years old from 60% -70%.[5] Treating HTN depends on the presentation of the patients and drugs for monotherapy includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and thiazide diuretics.[6] The etiology is still questionable because clear mechanism is still unclear. There is growing evidence that oxidative stress (OS) plays an important role in the etiology of HTN.[7] It is a common belief that OS is involved in various kinds of pathologic processes and diseases. Many major cardiovascular diseases are not an

exception in this regard. Hydrogen peroxide and superoxide radicals are important in the vascular system in particular. OS is therefore believed to have a major role in pathophysiology of HTN. There are strong experimental evidences to show that ROS are particularly involved in the diseased processes leading to develop HTN. The cause is hypothesized to be excess of $O_2^{\cdot -}$ and decreased bioavailability of Nitric Oxide in the vascular system and kidneys and also cardiovascular remodeling mediated by reactive oxygen species. Furthermore, biomarkers measured for systemic oxidative stress are elevated in HTN.[8, 9] Many antihypertensive drugs reduces oxidative stress along with normalization of blood pressure.[10] Losartan an ARB is considered as a 1st line therapy for HTN. Many animal studies reported that losartan reduces OS.[11,12] Similarly, losartan also reduces OS in salt induce HTN and hypoxia induce HTN but the results are limited in essential treatment naïve hypertensive patients.[13,14] The current study aimed to determine the effect of losartan on OS biomarkers in essential hypertension. The most reliable and easily detectable oxidant biomarker include serum MDA[15, 16], while anti-oxidants includes TAS, serum Ceruloplasmin and serum albumin.[15]

## Materials and Methods

This prospective cohort study was conducted in the department of medicine, Khyber teaching hospital Peshawar and department of biochemistry Khyber medical college Peshawar Pakistan. Total 200 newly diagnosed treatment naïve hypertensive patients of either gender were enrolled in the study. The duration of the study was 10 months started from March 2020 to Jan 2021. All the patients were guided about our research project and after willingness, proper consent forms were singed from all the patients. The demographics of each patient were recorded on purposefully design proforma. 5cc blood samples were withdrawn from each patient and rapidly distributed equally in EDTA and gel tubes. The blood tubes were properly labeled and transfer to the department of biochemistry for further analysis including blood glucose, renal function tests (RFTs), lipid profile, serum albumin and baseline oxidative stress markers including serum malondialdehyde, ceruloplasmin and total anti-oxidant status.

All patients were put on losartan 50mg once daily and followed for 30 days. After follow-up, the patients were re-examined and 5cc blood was extracted from each patients and transfer to the department of biochemistry for the above mentioned investigations. All the investigations were performed using manufacturer's protocols. The details of each kit are given below in table 1.

**Table 1: Detailed information of kits used in different assays**

| S.No | Kit Name | Company name | Catalog No |
|---|---|---|---|
| 1 | Glucose assay (enzymatic colorimetric test) | Human diagnostics GmbH Germany | 10260 |
| 2 | Urea assay (enzymatic colorimetric test) | Human diagnostics GmbH Germany | 10505 |
| 3 | Creatinine assay (kinetic colorimetric test) | Human diagnostics GmbH Germany | 10051 |
| 4 | Cholesterol assay (enzymatic colorimetric test) | Human diagnostics GmbH Germany | 10019 |
| 5 | Triglyceride assay (enzymatic colorimetric test) | Human diagnostics GmbH Germany | 10164 |
| 6 | High density lipoprotein (HDL) assay (enzymatic colorimetric test) | Human diagnostics GmbH Germany | 10018 |
| 7 | Albumin assay (Bromcresol green method) | Human diagnostics GmbH Germany | 10560 |
| 8 | Ceruloplasmin assay (Immunoturbidimetic test) | Wiener lab, Rosario Argentina | 1009357 |
| 9 | Total antioxidant status (TAS) assay | Gaziantep Turkey | RL0017 |
| 10 | Malondialdehyde (MDA) assay | Biovision USA | K739-100 |

LDL was calculated by using formula given by Friedewald et al. 1972.[17] LDL cholesterol (mg/dl) = total cholesterol – HDL cholesterol – (triglycerides/5). While VLDL was calculated by using the formula proposed by Wilson, cited by Delong et al. 1986.[18] VLDL-cholesterol = 0.2 × Triglycerides. All the numerical data was expressed as Mean ± SD while the categorical values were expressed as frequencies and percentages. The difference between all the values (initial and after 4th week) were compared using student t-test. P-value <0.05 were considered as significant. All the analysis were done using SPSS (Statistical package analysis package for the social sciences) version 20.0.

## Results

In total 200 hypertensive patients, 10 were loss during follow-up. Out of 190 patients 100 (52.6%) were males while 90 (47.4%) were females. The mean age was 45.35 ± 0.96 years. The mean BMI, SBP and DBP at the time of enrollment was 26.40 ± 0.36, 154.15 ± 0.71 and 93.54 ± 0.53 respectively. Similarly, the mean glucose, urea, creatinine and serum albumin before treatment were 92.71 ± 1.05, 24.98 ± 0.32, 0.96 ± 0.02 and 4.11 ± 0.03 respectively. The complete fasting lipid profile was done using standard method. The baseline triglycerides, serum cholesterol, HDL-c, LDL-c and VLDL-c were 178.46 ± 2.23, 247.77 ± 2.88, 36.71 ± 0.84, and 175.37 ± 3.10, 35.69 ± 0.45 respectively. Oxidative stress biomarkers including serum malondialdehyde (MDA), total antioxidant status (TAS) and serum ceruloplasmin were 3.63 ± 0.07, 1.42 ± 0.02 and 4.77 ± 0.06 respectively. All the parameters are summarized in table 2.

The enrolled patients were put on 50mg losartan and were followed for one month. After follow-up, all the parameters including BMI, systolic BP, diastolic BP, glucose, serum albumin, urea, creatinine, triglycerides, serum cholesterol, HDL-c, LDL-c, VLDL-c, MDA, TAS and serum Ceruloplasmin were re-evaluated to find any possible statistical difference. The analysis revealed that there is statistical significant difference between variables including systolic BP, diastolic BP, glucose, serum albumin, urea, triglycerides, serum cholesterol, LDL-c, VLDL-c, MDA, TAS and serum Ceruloplasmin with P-values < 0.001, < 0.001, < 0.001, 0.01, 0.02, < 0.001, < 0.001, < 0.001, < 0.001, < 0.001 and < 0.001 respectively as shown in table 3. All the differences are graphically shown in figure 1.

Legends: HDL: high density lipoprotein, LDL: low density lipoprotein, VLDL: very low-density lipoprotein, MDA: malondialdehyde, TAS: total antioxidant status, NS: non-significant

**Table 2: Description of study population**

| S. No. | Variables | Mean ± SD |
|---|---|---|
| 1. | Gender m/f | 100/90 |
| 2. | BMI (kg/m$^2$) | 26.40 ± 0.36 |
| 3. | Systolic BP (mmHg) | 154.15 ± 0.71 |
| 4. | Diastolic BP (mmHg) | 93.54 ± 0.53 |
| 5. | Glucose (mg/dl) | 92.71 ± 1.05 |
| 6. | Albumin (gm/dl) | 4.11 ± 0.03 |
| 7. | Urea (mg/dl) | 24.98 ± 0.32 |
| 8. | Creatinine (mg/dl) | 0.96 ± 0.02 |
| 9. | Triglycerides (mg/dl) | 178.46 ± 2.23 |
| 10. | Cholesterol (mg/dl) | 247.77 ± 2.88 |
| 11. | HDL-c (mg/dl) | 36.71 ± 0.84 |
| 12. | LDL-c (mg/dl) | 175.37 ± 3.10 |
| 13. | VLDL-c (mg/dl) | 35.69 ± 0.45 |
| 14. | MDA (µmol/l) | 3.63 ± 0.07 |
| 15. | TAS (mmol/l) | 1.42 ± 0.02 |
| 16. | Ceruloplasmin (gm/l) | (4.77 ± 0.06 |

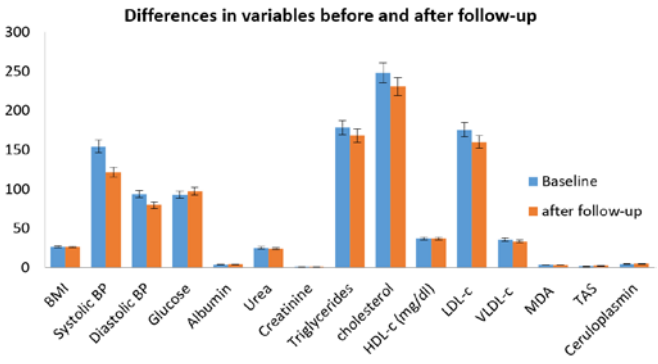


**Figure 1: Differences in study variables before and after follow-up**

**Table 3: Difference between study variables before and after therapy**

| S. No. | Variables | Baseline | After follow-up | P- value |
|---|---|---|---|---|
| | | Mean ± SD | Mean ± SD | |
| 1. | BMI (kg/m$^2$) | 26.40 ± 0.36 | 26.32 ± 0.35 | NS* |
| 2. | Systolic BP (mmHg) | 154.15 ± 0.71 | 121.61 ± 0.67 | < 0.001 |
| 3. | Diastolic BP (mmHg) | 93.54 ± 0.53 | 79.61 ± 0.44 | < 0.001 |
| 4. | Glucose (mg/dl) | 92.71 ± 1.05 | 97.40 ± 0.81 | < 0.001 |
| 5. | Albumin (gm/dl) | 4.11 ± 0.03 | 4.22 ± 0.03 | 0.01 |
| 6. | Urea (mg/dl) | 24.98 ± 0.32 | 23.86 ± 0.35 | 0.02 |
| 7. | Creatinine (mg/dl) | 0.96 ± 0.02 | 0.91 ± 0.02 | NS |
| 8. | Triglycerides (mg/dl) | 178.46 ± 2.23 | 167.89 ± 1.80 | < 0.001 |
| 9. | Cholesterol (mg/dl) | 247.77 ± 2.88 | 230.35 ± 2.39 | < 0.001 |
| 10. | HDL-c (mg/dl) | 36.71 ± 0.84 | 36.98 ± 0.75 | NS |
| 11. | LDL-c (mg/dl) | 175.37 ± 3.10 | 159.79 ± 2.61 | < 0.001 |
| 12. | VLDL-c (mg/dl) | 35.69 ± 0.45 | 33.58 ± 0.36 | < 0.001 |
| 13. | MDA (µmol/l) | 3.63 ± 0.07 | 3.19 ± 0.07 | < 0.001 |
| 14. | TAS (mmol/l) | 1.42 ± 0.02 | 2.12 ± 0.05 | < 0.001 |
| 15. | Ceruloplasmin (gm/l) | 4.77 ± 0.06 | 5.11 ± 0.07 | < 0.001 |

## Discussion

Losartan has already established anti-hypertensive effect due to blocking angiotensin II via type 1 (AT1) receptors.[19,20,21] Our study shows significant reduction of both SBP and SBP with p values <0.001 respectively. In consistent with our findings, a study published on evaluating the antihypertensive effect on 9193 patients reported significant reduction in both SBP and DPB.[22] Another study published in 2017 reported similar findings that shows significant reduction in HTN with once daily dose of losartan 50mg.[23]

Abrupt lipid profile is associated with adverse outcome in patient with HTN. Losartan is believed to normalize dyslipidaemia along with its anti-hypertensive effect. In our study, we found statistically significant reduction is triglycerides, total cholesterol, LDL and VLDL with p-values <0.001 respectively with a non-significant rise in HDL. Several studies in the last 25 years have been published reported similar findings in reducing triglycerides, total cholesterol, LDL and VLDL with once daily dose of losartan 50mg.[23,24,25,26]

The oxidative stress as discussed earlier is related to end organ damage in patient with HTN, the oxidative stress is measured by different biomarkers which are categorised as oxidants and anti-oxidants. Important, reliable and most easily detectable oxidant biomarker include serum MDA[15,16], while in anti-oxidants it includes TAS, serum Ceruloplasmin and serum albumin.[15] In our study we also evaluated the reduction in oxidative stress in hypertensive patients with losartan. According to our findings, Serum MDA levels were significantly reduces with one month losartan 50mg once daily therapy with p-levels <0.001. Similar findings were also reported by various researchers all over the world and this affect may be due to its blockage of AT1 receptors there by reducing the angiotensin induce oxidative stress.[26,27,28] Ceruloplasmin is an antioxidant synthesised in liver in response to tissue damage and inflammation. Increased Ceruloplasmin levels are found in patients with oxidative stress and is linked with end organ damages, metabolic syndrome and HTN.[29,30] In our study findings there is significant reduction in serum Ceruloplasmin levels with losartan 50mg once daily with p-value <0.001. According to a study published in 2007, the oxidative stress is greatly decrease with ARBs inhibitors in patients with diabetes.[31] Thus reduction in serum Ceruloplasmin levels in patients with HTN enhances patient's protection from complications including coronary artery diseases[32], heart failure [33]and metabolic syndrome.[29,30]

The albumin is abundantly found serum protein in humans. Sufficient levels of albumin is necessary for normal homeostasis there by scavenging free oxygen radicals and maintain microvascular integrity[34]. The albumin shows its anti-oxidant activity by blocking the copper ion-dependent generation of hydroxyl radicals and lipid peroxidation.[35] In our study, we found significant increase in serum albumin levels after one month treatment with losartan 50mg once daily with p-value 0.01. Losartan has found to

decrease protein excretion[36, 37], decreases progression of nephropathy [38] thus provides long term benefits to patient with essential HTN and HTN associated with metabolic syndromes.

The total antioxidant status (TAS) was found low in our enrolled newly diagnosed hypertensive patients, consequently the oxidative stress is relatively high in these patients as compared to normal patients as reported earlier[39]. After administration of losartan 50 mg once daily, the TAS levels were significantly increased (p-value= <0.001) as reported by other researchers too. [40]

## Conclusion

Apart from its antihypertensive properties, losartan is also effective in reducing oxidative stress and lipid profile thus provides long term beneficial effects on reducing complications associated with HTN.

**Conflict of Interest:** Authors declare no conflict of interest.

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| Mudasir Ahmad Khan | B,C |
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C. Interpretation/ Analysis and Discussion