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Research Article

COMPARATIVE ANALYSIS OF EFFECT OF ACE INHIBITOR AND BETA BLOCKERS ON OXIDATIVE STRESS, INSULIN RESISTANCE AND CARDIOVASCULAR RISK FACTORS IN ESSENTIAL HYPERTENSION

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ABSTRACT

Background: *Hypertension is a multi-factorial process, prevalent in developed as well as in. developing countries. Several studies have reported that, redox imbalance and insulin resistance are closely related in pathogenesis of essential HTN. However, the effect of antihypertensive drugs on these parameters is not well studied.*

Aims: *The aim of the study was to compare the effects of antihypertensive treatment with enalapril and atenolol on oxidative stress and insulin resistance in patients with essential hypertension.*

Materials and Methods: *57 freshly diagnosed essential hypertensive patients and 28 normotensive subjects in the age group of 30-60 years were enrolled for this study .Oxidative stress parameters and insulin levels were studied before and two months after treatment with enalapril 31 patients and atenolol in 26 patients.*

Results and Discussion: *We found that, SBP, DBP, oxidative stress and insulin resistance were significantly higher in hypertensive patients as compared to control subjects. Treatment with enalapril reduces SBP, DBP, oxidative stress and insulin resistance and improves antioxidant system and insulin resistance more significantly than atenolol treatment. We also found that, treatment with enalapril beneficially modified the lipid profile more significantly than atenolol. Insulin resistance in essential hypertension may be due to the increased oxidative stress through enhanced angiotensin II activity. The beneficial effect of the enalapril (ACE-inhibitor) compared to atenolol (beta blocker) on insulin sensitivity, could be due to preservation of redox imbalance by inhibiting angiotensin II.*

Conclusion: *Enalapril treatment reduces oxidative stress, coronary lipid risk factors and improves insulin signaling more effectively than atenolol in essential hypertension*

KEYWORD: *Cardiovascular risk factors, ACE inhibitors, Enalapril, Insulin Resistance.*

INTRODUCTION

Hypertension is a multi-factorial process, prevalent in developed as well as in developing countries [1] (Kashyap MK et al 2005). Hypertension is characterized by a sustained elevation of systolic blood pressure of greater than 140 mm Hg and a diastolic blood pressure of greater than 90 mm Hg. In about 80% of the patients, the cause of the hypertension is unknown and it is called *essential hypertension* [2] (Laragh JH, et al 1983). Hypertension can result from either an increased cardiac output or increased peripheral resistance or both. At present, essential hypertension is treatable but not curable. Effective lowering of the BP has been effected by drugs that block alpha-adrenergic receptors either in the peripheral or in the central nervous system, beta-blocker, angiotensin converting enzyme inhibitors and calcium channel inhibitors (William F.Ganong 2006) [3]. Compared to the normal subjects, the essential hypertensive patients have increased oxidative stress [4]. (Ward NC et al 2006). Whether oxidative stress

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precedes hypertension or hypertension precedes oxidative stress is still unknown.

Insulin resistance and hypertension are common disorders that are closely related. Insulin resistance (IR) is defined as an impaired metabolic response to either exogenous or endogenous insulin, which results in a higher plasma insulin concentration than would be expected for the existing plasma glucose. Among several factors, oxidative stress has been reported to be intimately related to insulin resistance (Rudenski AS et al 1999) [5]. Several studies in vitro have demonstrated that reactive oxygen species (ROS) can cause insulin resistance by several mechanisms, such as altered serine/tyrosine phosphorylation leading to inhibition of insulin receptor substrate-1 (IRS-1) phosphorylation and inactivation of phosphatidylinositol (PI)-3 kinase activities. All these effects lead to inactivation/inhibition of other substrates involved in the insulin signaling pathway like protein kinase B (PKB), IP3, Grb2 etc and thereby causing insulin resistance (Haffiier, S. M. 2000). Folli et al reported that, increased angiotensin II in essential hypertension inhibits the insulin signaling pathway in aortic smooth muscles at multiple levels such as inhibition of phosphatidylinositol (PI)-3 kinase activation associated with IRS-1 (Haffner, S. M. 2000).

Studies also reported that, treatment with ACE inhibitors improves the insulin resistance whereas the beta blockers cause insulin resistance. Administration of ACE inhibitor reduces the angiotensin II formed from angiotensin I by ACE that may reduce the oxidative stress and altered serine/tyrosine phosphorylation which causes insulin resistance Haffner, S. M. 2000) [6].

MATERIALS AND METHODS

A prospective study was conducted, Rajah Muthiah Medical College is a medical college in Chidambaram, Cuddalore district, Tamil Nadu, India. After obtaining the ethical committee permission. Subjects were classified as normotensive (or control) and hypertensive as per the recommendation of the JNC 7 report. Fifty freshly diagnosed essential hypertensive patients and twenty normotensive subjects in the age group of 30-50 years were enrolled for this study. Subjects with a history of diabetes, renal disease, endocrine dysfunction, coronary artery disease, infections, smokers, alcoholics and those who are on any kind of medications were excluded from the study. A written informed consent was obtained from the subjects. The study was approved by the research and ethics committee of our institute.

Blood sample collection:

On the day of study, subjects reported to our laboratory in the morning after an overnight fasting of 12 hours. Five ml of venous blood was collected. The whole blood was used for the estimation of glutathione and hemoglobin. Plasma was collected by centrifuging rest of the sample at 3000g for 5 min at 4°C and was used for the estimations of malondialdehyde, protein carbonylation, total antioxidant capacity, insulin and lipid profile. The erythrocytes separated were used for the estimation of antioxidant enzymes (catalase and glutathione peroxidase) and remaining plasma stored at -70°C until analysis.

Anthropometric measurements:

Height and weight were measured by using a standardized protocol, and BM1 was calculated as weight in kilograms divided by square of height in meters.

Analysis of plasma biochemical parameters: Plasma glucose and lipid profile were estimated in the fasting samples using standard reagent kits adapted to the 550 Express Plus clinical chemistry analyzer (Bayer's Diagnostics, USA). Fasting plasma insulin was estimated using human insulin ELISA kit following manufacture (United Biotech Inc, USA) instructions. From the fasting glucose and insulin values the homeostatic model assessment-insulin resistance (HOMA-IR) was calculated using the following formula (Pickavance. 2001). HOMA-IR = fasting insulin (|jU/ml) X fasting glucose (mM/L)/22.5.

Analysis of oxidative stress parameters: The *plasma MDA* was estimated by the method of Yagi (Yagi. 1984). To 0.5 ml of plasma, 2.5 ml of trichloroacetic acid (20% TCA) was mixed and incubated at room temperature for 10 minutes. The mixture was centrifuged at 3500g for 10 minutes at room temperature. The supernatant was discarded and the precipitate was washed twice with 0.05M H2SO4. The precipitate was suspended in 2.0ml of 0.05M H2SO4 and 3.0 ml of thiobarbituric acid (TBA) reagent (0.22% TBA in 2M Na2S04 solution) was added. This mixture was incubated in a boiling water bath for lhour. After 1 hour, the tubes were cooled under running tap water and mixed thoroughly with 4.0 ml of butanol. The tubes were centrifuged at 3500g for 15 minutes at room temperature. The absorbance of butanol layer was measured at 530nm. The concentration of MDA was calculated using the molar extinction co-efficient (1.56 X 10^5) and expressed as pMols/L. The *plasma protein carbonyl contents* were measured according to the modified Levines method by Chakroborthy. Test- To 0.1ml plasma, 0.9ml distilled water was added and mixed well. To this 1.0ml 2, 4- DNPH was added and incubated at room temperature in dark for lhr.To this 4.0ml 10% TCA was added and centrifuged at 3500g for 5min and the pellet was washed 3 times with 2.0ml ethanol: ethyl acetate and this was dissolved in 2.0ml protein dissolving solution. Blank- To 0.1ml plasma, 0.9ml distilled water was added and mixed well. To this 1.0ml 2M HC1 was added and incubated at room temperature in dark for 1 hr.The rest of procedure was same as the test. The color developed was measured at 366nm.

The *whole blood reduced glutathione* content was determined by the method of Beutle et al. To 0.2 ml of whole blood, 1.8 ml of distilled water and 3.0 ml of precipitating solution (5% TCA and ImM EDTA) were added and mixed. This mixture was incubated at room temperature for 10 minutes. The mixture was centrifuged at 3500g for 10 minutes. To 1.5 ml of the supernatant, 2.5 ml ofNa2HPC>4 (0.3M) and 3.0 ml of dithionitro benzoic acid (0.4% DTNB and 1% sodium citrate) were added. This mixture was incubated at room temperature for 30 minutes. After 30 minutes of incubation the absorbance was measured at 412nm. A standard graph was drawn using reduced glutathione as standard and the reduced glutathione concentration in the samples were calculated. The *hemoglobin content* of the blood was estimated using Drabkin's solution following manufacturer's instructions. The reduced glutathione values were expressed as mg/g Hb. The *catalase activity in erythrocytes* was estimated by the method of Aebi. Red blood cells (RBC) were separated from the blood by centrifuging at 3500g for 10 minutes at 4°C. RBC pellet was washed three times with ice-cold PBS. RBC lysate was prepared by adding 0.1 ml of RBC to 0.4 ml of distilled water. 20(^1 of RBC lysate was further diluted in 10 ml of phosphate buffer (50mM KH2PO4 and

50mMNa2HP04, pH 7.0). Catalase assay was performed by adding 1.0 ml of 30mM H2O2 to 2.0 ml of diluted RBC lysate. The decomposition of H2O2 was measured by monitoring the decrease in the absorbance at 240nm for 60 seconds. The catalase activity was expressed as rate constant (k/ml). The *glutathione peroxidase activity in erythrocytes* was estimated by Wendel et al method. The RBC pellet was separated by centrifuging the blood at 3500g for l Omin. The enzyme lysate was prepared by mixing 0.1ml pellet with 0.4ml distilled water and 0.5ml Drabkin reagent. The reaction mixture was prepared by taking 2.0ml buffer, 0.5ml sodium azide, 0.5ml EDTA, 0.5ml GSH, 1.0ml distilled water and 0.1ml enzyme lysate in four tubes marked as 0, 1,2 and 3.Then, 1.0ml hydrogen peroxide was added in all the tubes at every lmin interval. Finally, 2.0ml precipitating solution and 2.0ml DTNB were added in all the tubes and incubated at room temperature for 30min and read at 412nm.The values are expressed in U/g Hb.

Antihypertensive treatment: The essential hypertensive patients were followed after two months of treatment with ACE-inhibitor enalapril (l0 mg/day) and beta blocker atenolol (25mg/day) and all the above parameters were studied.

Statistical analysis: Results were shown as Mean ± SD. Statistical significance of difference between control, hypertensive patients with before treatment and two months after treatment was evaluated using *one way ANOVA analysis by Tukey method* . Correlation between the clinical parameters was estimated by *Pearson's Correlation Co-efficient.* A P-value less than 0.05 were considered statistically significant. All calculations were performed using the SPSS version 13.0 for windows.

RESULTS

Table 1 shows that, the SBP, DBP, fasting plasma glucose and fasting plasma insulin were significantly higher in essential hypertensive patients as compare to control subjects. Both enalapril and atenolol significantly reduces the SBP and DBP. The enalapril significantly reduces the fasting plasma glucose and insulin whereas atenolol significantly increases the fasting plasma insulin level. We also observed that enalapril reduces SBP and DBP, more significantly than atenolol.

Table 2 shows that, the plasma MDA, protein carbonyl contents gluthathione peroxidase and HOMA-IR were significantly higher in hypertensive patients as compared to controls. Whereas GSH, catalase and TAC were significantly lower in essential hypertensive patients. Both enalapril and atenolol significantly reduce plasma MDA and protein carbonyl contents but enalapril reduce more significantly than atenolol. We also found, enalapril significantly reduces the gluthione peroxidase, HOMA-IR and significantly increases the GSH, catalase, and TAO as compared to before treatment. Whereas atenolol significantly reduce the GSH and significantly increase the HOMA-IR as compare to before treatment.

Table 3 shows that, the cholesterol and LDL-cholesterol were significantly higher and HDL cholesterol was significantly lower in hypertensive patients as compared to controls. The enalapril reduce the triglycerides, LDL-cholesterol and increases the HDL-cholesterol significantly as compared to atenolol. Whereas, the atenolol increases the triglycerides, LDL-cholesterol and decrease the HDL-cholesterol (not significant) as compared to control.

The TC/HDL ratio, LDL/HDL ratio and non HDL cholesterol were significantly higher in hypertensive patients as compared to controls. The enalapril significantly reduces the TC/HDL ratio and LDL/HDL ratio. Whereas, atenolol significantly increases the LDL/HDL ratio as compared to the before treatment.

Table 4 shows that, there are significant negative correlation between GPx – catalase and catalase - HOMA-IR and significant positive correlation between GPx-HOMA-IR.

Table No. 1: General and biochemical characteristics of controls and hypertensive patients before and after treatment

	Parameters	Control (N=20)	Enalapril group (N = 25)		Atenolol group (N = 25)	
			Before	After	Before	After
1	Age (Years)	39.1±6.4	38.4±5	38.4 ± 5	38.6 ± 5.5	38.6 ± 5.5
2	BMI (Kg/m²)	23.7±2.6	25.6±3.1	25.5 ± 3.1	25.3 ± 2.5	25.2 ±2.5
3	SBP (mmHg)	105.1±12.8	165.9±19.8[a]	115.5±11.2[b]	167.7±18.1[a]	127.3±6.8[c]
4	DBP (mmHg)	71.1±7.9	99.8±5.7[a]	72.4±6.5[b]	100.2±5.4[a]	78.6±4.8[cd]
5	Fasting plasma glucose (mg/dL)	81.6±11.8	97.6±4.9[a]	85.2±9.8[b]	90.4±14.1[a]	94.5±9.5
6	Fasting plasma Insulin (μU/mL)	24.7±10.8	49.1±34.6[a]	22.5±17.1[b]	36.3±30.9[a]	47.9±32.7[cd]

a, b, c, d, P < 0.05 is statistically significant (*a – Comparison between control group and hypertensive patients in both groups; b – Comparison between before and after enalapril treatment of patients; c – Comparison between before and after atenolol treatment of patients; d – Comparison between after enalapril treatment of patients and after atenolol treatment of patients****)***

Table No. 2: Oxidative stress parameters and insulin resistance of controls and hypertensive patients before and two months after treatment

	Parameters	Control (N=20)	Enalapril group (N = 25)		Atenolol group (N = 25)	
			Before	After	Before	After
1	GSH (mg/g Hb)	4.4±0.6	2.8±0.5[a]	3.0±0.8[b]	2.4±0.5[a]	1.3±0.4[c d]
2	GPx (U/g Hb)	57.8±18.8	90.6±10.5[a]	74.1±9.1[b]	88.8±9[a]	86±7.6[d]
3	Catalase (k/ml)	32.3±8.8	27±3.4[a]	33.4±3.7[b]	27.5±3.7[a]	26.1±2.8
4	MDA (μmol/L)	2.5±0.9	4.9±0.9[a]	2.3±0.7[b]	5±1.2[a]	3.8±0.9[c d]
5	Protein Carbonyls (nmol/mg)	2.2±0.8	5.5±1[a]	2.4±0.9[b]	5.5±1[a]	3.6±0.7[c d]

6	HOMA-IR	4.9±2.3	12.6±8.9[a]	4.6±3.3[b]	8±6.9[a]	11.1±7.8[c d]
7	Plasma TAC	1598.8± 496.1	1343.1± 416.7[a]	1819.5± 477.5[b]	1314.6± 297.4[a]	1675.9± 361.64[c d]
8	Plasma free sulfhydryl group (mg/dl)	498.7± 215	399.7± 260	523.5± 253.8[b]	387.9± 124.7	470.5± 260.4[c d]

a, b, c, d, P < 0.05 is statistically significant (*a – Comparison between control group and hypertensive patients in both groups; b – Comparison between before and after enalapril treatment of patients; c – Comparison between before and after atenolol treatment of patients; d – Comparison between after enalapril treatment of patients and after atenolol treatment of patients****)***

Table No. 3: Lipid profile, coronary lipid risk factors and plasma protein bound sialic acid of controls and hypertensive patients before and two months after treatment

	Parameters	Control (N=28)	Enalapril group (N = 31)		Atenolol group (N = 26)	
			Before	After	Before	After
1	Total cholesterol (mg/dL)	168.4±34.3	195±40.9[a]	175.7±22.2	190.4±37.3	197±30.7[d]
2	TG (mg/dL)	127.7±88.9	136±38.9	122.6±32.4[b]	137.6±46.8	142.8±55.5[d]
3	HDL – Cholesterol (mg/dL)	49.7±9.7	36.9±3.7[a]	42.2±4.9[b]	39.1±6.6[a]	38.9±4.7
4	LDL – Cholesterol (mg/dL)	94±34.7	125.7±36.1[a]	100.9±22.9[b]	122.1±36.5[a]	133.6±28[d]
5	VLDL – Cholesterol (mg/dL)	25.4±17.7	27.5±7.1	24.5±6.5	27.7±8.9	27.9±11.1
6	TC/HDL	3.9±1.7	5.5±1.7[a]	4.2±0.8[b]	5.1±2[a]	5.1±0.5
7	TG/HDL	0.1±0.07	0.2±0.07	0.1±0.03	0.2±0.06	0.2±0.1
8	LDL/HDL	2.3±1.4	3.5±1.4[a]	2.5±0.8[b]	3.4±1.7[a]	3.4±0.5[c]
9	NHC(TC-HDL)	31.7±11.1	40.1±11.5[a]	34.5±6.3	39.2±11.2[a]	40.9±6.9
10	Atherogenic index	-0.9±0.2	-0.8±0.1[a]	-0.9±0.1	-0.8±0.2[a]	-0.8±0.1
11	Plasma protein bound sialic acid (µg/mg)		4.9±1.2	4.1±0.99[b]	5.2±1.3	4.7±1.1

a, b, c, d, P < 0.05 is statistically significant (*a – Comparison between control group and hypertensive patients in both groups; b – Comparison between before and after enalapril treatment of patients; c – Comparison between before and after atenolol treatment of patients; d – Comparison between after enalapril treatment of patients and after atenolol treatment of patients****)***

Table No. 4: Correlation coefficient among GPx, GSH, catalase and HOMAIR in hypertensive patients

	GPx	CATALASE	HOMA-IR
GSH	-0.021	0.039	-0.076
GPx		-0.919**	0.631**
CATALASE			-0.496**

***** Correlation is significant at the 0.01 level (2-tailed)***

DISCUSSION

Oxidative stress is intensified with the process of aging, and in the elderly, this is accompanied by more common occurrence of primary hypertension [Mollanau H et al 2002. An excessive ROS concentration, especially hydroxyl radical, has been found in patients with essential arterial hypertension. ROS induces lipid peroxidation, increased disulfide / sulfhydryl ratios and modification of amino acid residues to carbonyl derivatives in the protein [Esterbuer H et al 1991].

All membranes are characterized by the large amounts of PUFA associated with amphipathic lipids. Peroxidation of these labile unsaturated fatty acids can damage both proteins and lipids [Esterbuer H et al 1991]. Peroxidation is autoxidation of lipids exposed to oxygen radicals. Chemicals processes involved in peroxidation are initiation, propagation and termination. During chain propagation reaction, the lipid perooxyl radicals can form cyclic peroxides. This then decomposes to a number of breakdown products such as Malondialdehyde. There products can react with DNA and are mutagenic [Esterbuer H et al 1991].

Reactive oxygen species can modify the amino acids of proteins and lead to cross linking changes in conformation and loss of functions. Irreversible oxidative damage occurs to susceptible amino acids like tryptophan and histidine by ring cleavage. Proteins having vulnerable amino acids are highly susceptible to oxygen radicals, undergoing irreversible changes of protein conformation [Simpson ja et al 1992]. Several studies reported that, lipid peroxidation and protein carbonylation are the important factors for the pathogenesis of primary hypertension [Higashi Y et al 2001] [9].

In this study, we observed that, the lipid peroxidation and protein carbonylation were significantly lower in enalapril treated patients as compared to atenolol treated patients. It indicates that, the enalapril more significantly reduces the lipid peroxidation and protein carbonylation than atenolol. this may be due to inhibition of ACE and generation of Ang-II (vasoconstrictor) by enalapril but not by atenolol. Ang-II activates the membrane-bound NADH and NADPH oxidases [Higashi Y et al 2001]. The increased vascular activity of NADH and NADPH oxidase enhances the production of reactive oxygen species by several pathways, including the increased activation of xanthine oxidase, the auto-oxidation of NADH and the inactivation of superoxide dismutase [Higashi Y et al 2001]. Thus, enhanced production of reactive oxygen species causes an increased protein carbonylation and lipid peroxidation. Enalapril inhibits the ACE and generation of Ang-II and these may decrease the protein carbonylation and lipid peroxidation more effectively than atenolol. Previous studies also suggest

that, ACE-inhibitors reduce angiotensin II more significantly than beta-blockers. This help in the reduction of oxidative stress in essential hypertension [10]. In the present study, we observed that, the erythrocyte catalase and whole blood glutathione activities were decreased and glutathione peroxidase activity was increased in hypertensive patients as compared to controls. The increased activity of glutathione peroxidase may be compensated by the decreased activities of catalase. The increased erythrocyte glutathione activity in hypertensive patients also supports the free radical mediated injury in them. Glutathione peroxidase is a selenium containing enzyme having a single seleno-cysteine residue in each of the four identical subunits, which are essential for enzyme activity [11] [J.M. Mates et al 1999]. The primary catalytic cellular defense that protects calls and tissues against lipid peroxidation is the glutathione peroxidase enzyme [12] [D.Lu et al 1993]. Glutathione peroxidase shares the substrate hydrogen peroxide with catalase but it alone reacts effectively with lipids and other organic hydroperoxides [13] [C. Michieles et al 1990]. Glutathione peroxidase expression is rapidly increased in some conditions, when cells or organisms are exposed to oxidative stress. The increased erythrocyte glutathione peroxidase activity in hypertensive patients may be interpreted as a compensatory mechanism due to increased lipid peroxidation. Because glutathione peroxidase is more potent on a molar basis than other antioxidant enzymes in protecting cells from oxidative stress. However, the marked increase in this enzyme is not sufficient to protect cells from oxidative stress, since increased MDA and carbonyl contents were also seen [V. Sathiyapriya et al 2007].

After treatment with enalapril, the erythrocyte GPx was significantly reduced, whereas the glutathione and catalase activities significantly increased as compared to before treatment. The increased activities of catalase may be compensation the decreased activity of GPx. This suggests that, there is a negative relationship between catalase and GPx. Our present study also supports this because we got a negative correlation between catalase and GPx. Catalase is tetrameric enzyme containing four identical subunits, each subunit contain ferri protoporphyrin group. Catalase protects cells from hydrogen peroxide generated within the cell [14] [V. Sathiyapriya et al 2007]. The atenolol treatment reduces the glutathione level significantly as compared to before treatment patients. No significant differences were observed in the levels of catalase and glutathione peroxidase.

Insulin resistance and hypertension are common disorders that are closely related. Among several factors, oxidative stress has been reported to be intimately related to these diseases. Several studies *in vitro* have demonstrated that reactive oxygen species (ROS) can cause insulin resistance by several mechanisms, such as altered tyrosine/serine phosphorylation leading to inhibition of insulin receptor substrate-I (IRS-I) function and inactivation of phosphatidylinositol (PI)-3 kinase activities. All these effects lead to inactivation / inhibition of other substrates involved in the insulin signaling pathway like protein kinase B (PKB), IP3, Grb2 etc and thereby causing insulin resistance reported that increased angiotensin II in essential hypertension inhibits the insulin signaling pathway in aortic smooth muscles at multiple levels such as inhibition of phosphatidylinositol (PI)-3 kinase activation associated with IRS-1 [15].

Several studies have reported that treatment with ACE inhibitors improves the insulin resistance. Administration of ACE inhibitor reduces the angiotensin II formed from angiotensin I by Ace. This in turn may reduce the oxidative stress and serine/tyrosine phosphorylation and such a mechanism does not exist for the action of atenolol [16].

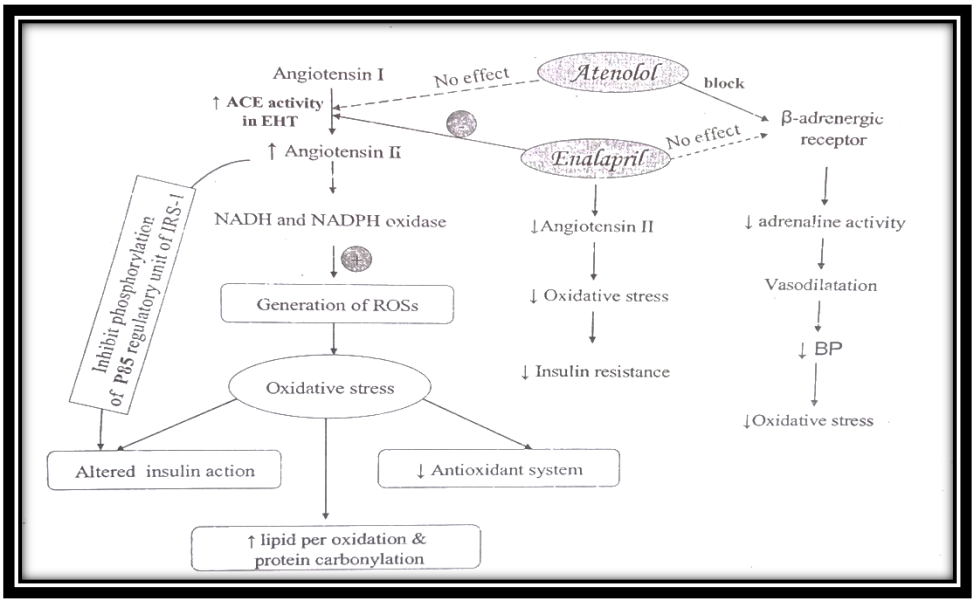

Fig. 1: Effect of enalapril and atenolol on oxidative stress and insulin resistance in essential hypertension

Previous studies have reported that, hypertension patients had higher total cholesterol, low-density lipoprotein cholesterol, triglycerides, body mass index and low high-density lipoprotein cholesterol levels than normotensive subjects. The elevated lipid peroxidation and lipid profile may contribute to the propensity in such patients to develop cardiovascular disease. In this study, we also observed that, the total cholesterol and LDL-cholesterol were significantly higher and HDL-cholesterol was significantly lower in hypertensive patients as compared to controls. In hypertension, increased ROS production causes the modification of LDL-cholesterol to oxidized LDL. This modified LDL have higher half life than normal LDL-cholesterol. This leads to increase plasma LDL-

cholesterol. This in turn may lead to the formation of foam cells [17].

In this study, we also observed that, the enalapril reduces the total cholesterol, LDL-cholesterol and increases the HDL-cholesterol significantly as compared to atenolol. Furthermore, atenolol treatment increases the total cholesterol, LDL-Cholesterol and decreases the HDL-cholesterol as compared to controls. Whereas enalapril increases the HDL-cholesterol as compared to before treatment. The increased total cholesterol, LDL-cholesterol and decreased HDL-cholesterol are risk factors for the development of atherosclerosis [18, 19].

We also found that the TC/HDL ratio, LDL/HDL ratio and non HDL cholesterol were significantly higher in hypertensive patients as compared to controls. The enalapril significantly reduces the TC/HDL ratio and LDL/HDL ratio. Whereas, atenolol significantly increases the LDL/HDL ratio as compared to before treatment [20]. This indicates enalapril reduces the coronary lipid risk factors and such a mechanism does not exist for the action of atenolol.

CONCLUSION

Our results suggest that, the enalapril therapy beneficially modifies the lipid profile and reduces coronary lipid risk factors significantly than atenolol. Furthermore, enalapril reduces oxidative stress and improves insulin action more effectively than atenolol in essential hypertension. Enalapril treatment reduces oxidative stress, coronary lipid risk factors and improves insulin signalling more effectively than atenolol in essential hypertension.

REFERENCES:

1. Kashyap MK, Yadav V, Sherawat BS, Jain S, Kumari S, Khullar M, Sharma PC, Nath R. Different antioxidants status, total antioxidant power and free radicals in essential hypertension. Mol Cell Biochem **2005**;277(1-2):89-99.
2. Gavras, Haralambos, Brunner, Hans R. Laragh, John H. An Angiotensin Converting-Enzyme Inhibitor to Identify and Treat Vasoconstrictor and Volume Factors in Hypertensive Patients, N Engl J Med **1974**;291:817-821 doi:10.1056/nejm197410172911603.
3. William f. Ganong, Kazuharu Murakami. The Role of Angiotensin II in the Regulation of ACTH Secretiona. Annals of the New York Acad of Sci **2006**;512(1):176–186. DOI: 10.1111/j.1749-6632.1987.tb24959.x,
4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **1985**;28:412-419.
5. Haffner SM. Clinical relevance of the oxidative stress concept. Metabolism **2000**;49:30-34.
6. Halliwell B. Free radicals, proteins and DNA: oxidative damage versus redox regulation. Biochem Soc Trans **1996**;24:1023-1027.
7. Mollnau H, Wendt M, Szocs K, et al. Effects of angiotensin infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/'cGMP signaling. Circ Res **2002**;90:E58-E65.
8. Esterbuer H, et al. Chemistry and biochemistry of hydroxyl non-enol malondialdehyde and related aldehydes. Free Radical Bio Med **1991**;11:81-128.
9. Higashi Y, et al. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med **2002**;346: 1954-62.
10. Ritz E, Haxsen V. Angiotensin II and Oxidative Stress: An Unholy Alliance. J Am Soc Nephrol **2003**;14:2985-2987.
11. Mates JM, Perez-Gome C, Nunze de Castro I. Antioxidant enzymes and human diseases. Clin Biochem **1999**;32: 595-603.
12. Lu D, Maulik N, Moraru IL, Kreutzer DL, Das DK. Molecular adaptation of vascular endothelial cells to oxidative stress. Am J Physiol **1993**;264:C715-C722.
13. Michieles C, Toussaint O, Remade J. Comparative study of oxygen toxicity on human fibroblast and endothelial cells. J Cell Physiol **1990**;144:295-302.
14. Sathiyapriya V, Selvaraj N, Bobby Z, Apama A. Perturbation of erythrocyte antioxidant barrier, lipid peroxidation and protein carbonylation in non-diabetic first degree relatives of patients with type 2 diabetes. Diabet Res Clin Pract **2007**;35:167-178
15. Folli F, Saad MJ, Backer JM, Kahn CR. Regulation of phosphatidylinositol 3-kinase activity in liver and muscle of animal models of insulin-resistant and insulin-deficient diabetes mellitus. J Clin Invest **1993**;92:1787-1794.
16. Folli F, Khan CR, et al. Angiotensin II inhibits the insulin signaling in aortic smooth muscles at multiple levels: a potensial role of serine Phosphorylation in insulin/angiotensin crosstalk. J Clin Invest **1997**;100: 2158-2169.
17. Aebi H. Catalase in vitro. Methods Enzymol **1984**;105: 121-126.
18. Digiesi V, et al. Reactive metabolites of oxygen, lipid peroxidation, total antioxidant capacity and vitamin E in essential arterial hypertension. Clin Ter **1997**;148:515.
19. Rajagopalan S, Kurz S, Munzel T, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contributions to alterations of vasomotor tone. J Clin Invest **1996**;97:1916.
20. Griendling KK, Minieri CA, Ollerenshaw D, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res **1994**;74:1141-8.
21. Lewis TS, Shapiro PS, Ahn NG. Signal transduction through MAP kinase cascades.In: Woude GFV, Klein G, eds. Advances in cancer research. San Diego: Academic PressInc **1998**;74:49-139.

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