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The effects of Losartan on oxidative stress and inflammation in non-diabetic patients undergoing chronic hemodialysis

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Abstract. – INTRODUCTION: We aimed to evaluate the effects of Losartan, an angiotensin receptor blocker, on serum inflammatory markers, plasma thiol groups, and oxidative stres indexes among patients undergoing hemodialysis (HD) treatment.

PATIENTS AND METHODS: Fiftytwo end-stage renal disease (ESRD) patients undergoing chronic HD programme for at least 12 months, and thirty age and gender matched healthy volunteers were enrolled into this prospective clinical trial. Plasma levels of thiol groups (SH), total antioxidant capacitiy (TAC), and total oxidant status (TOS) were studied. Oxidative stress index (OSI) was calculated by TOS/TAC. Firstly results of patients were compared with healthy subjects and then patients were treated by Losartan 50-100 mg and followed up for three months.

RESULTS: Among patients, SH Groups, TAC, TOS, and OSI were statistically higher than controls. Also the inflammatory markers were significantly higher in patients than controls and albumin was lower among patients. At the end of the 3 months among all patients the mean value of TAC was increased to 1.7±0.4 micromol Trolox Eqv./L. from 1.4±0.2, and SH groups to 0.33±0.02 mmol/L from 0.22±0.01, ($p < 0.001$) while TOS decreased to 7.2±1.1 micromol H_2O_2 Eqv./L from 9.5±4.5, and OSI decreased to 5.0±0.8 from 7.1±3.2 ($p < 0.001$).

CONCLUSIONS: Losartan was effective in controlling blood pressure, and decreasing OSI, a marker of elevated oxidative stress, and increasing plasma levels of SH groups, an antioxidant, in ESRD patients undergoing hemodialysis. So, it may not be only a hypotensive drug, but also improves OS, particularly in patients with ESRD.

Key Words:
Hemodialysis, Losartan, Oxidative stres, Inflammation.

Introduction

Cardiovascular events (CVE) are the main causes of death in patients with end-stage renal disease (ESRD)[1,2]. According to two of the largest ESRD registries, the US Renal Data System (USRDS) and the European Registry of patients on renal replacement therapy (ERA-EDTA), among these patients the estimated risk for CVE is 3.5-50 times higher than in the general population[3,4]. This elevated risk is associated with both classical cardiovascular and uremia-specific risk factors, such as chronic hypervolemia, secondary hyperparathyroidism, anemia, hyperhomocysteinemia, excess inflammatory status with increased oxidative stress. These non-traditional risk factors are being given emphasis not only because of explanation of the high prevalence of CVE among patients with ESRD[5], but also because they may represent newer targets for therapeutic intervention.

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are giving researchers cause to hope to decrease morbidity and mortality in patients undergoing dialysis. In recent study we aimed to evaluate the effects of an ARB, Losartan, on oxidative stress [plasma thiol groups (SH), total antioxidant status, and oxidative stres index (OSI)] and acute phase reactants [C-Reactive protein (CRP), ferritin, and fibrinogen] among patients undergoing chronic hemodialysis (HD).

Patients and Methods

Sixty non-diabetic ESRD patients on chronic HD programme, for at least 12 months, and 30 healthy age and gender matched volunteers as control group were included into the study. All the patients were treated by conventional bicarbonated HD for 5 hours thrice weekly using low-flux hollow-fiber dialyzers (Polysulfone membrane, Fresenius Medical Care, Bad Homburg, Germany). The study was designed as a prospec-

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tive, clinical trial for a period of 3 months with two phases. The first phase was planned as comparison between the baseline values of patients and healthy group, and the second phase was planned as follow up period of patients treated with Losartan for three months and comparing the last values with beginnig. Patients with chronic inflammation/infection diseases (such as rheumatoid arthritis, tuberculosis, etc), chronic heart failure, and uncontrolled hypertension were excluded. Patients who were using calcium channel blockers were shifted to Losartan 48 hours after cessation of previous drug, and patients who were using ACE inhibitors or ARBs were shifted to Losartan after a wash out period of a week. Blood pressure of patients were closely controlled during wash out period and calcium channel blocker were used when required. Written informed consent were taken from all patients and then all of them treated with Losartan potassium 50-100 mg/day due to their blood pressure levels, and followed up for 3 months.

Age, gender, and dialysis duration of patients were recorded from dialysis centre records. Serum biochemistry and complete blood counts were studied. Plasma levels of TAC, TOS, and SH groups were studied from the samples taken after 12 hours fasting period, before HD session. Blood pressure of all patients were measured before dialysis session after at least 15 minutes resting, and mean of two sequential measurement was recorded.

Total antioxidant status of plasma was determined using a novel-automated measurement method, developed by Erel[6]. In this method, hydroxyl radical, which is the most potent biological radical, is produced. In this assay, antioxidative effect of the sample against the potent free radical reactions, which is initiated by the produced hydroxyl radical, is measured. The assay has got excellent precision values, which are lower than 3%. The results are expressed as mmol Trolox equivalent/l.

Total peroxide concentrations of plasma samples were determined using the FOX2 method[7] with minor modifications[8]. The FOX2 test system is based on oxidation of ferrous ion to ferric ion by various types of peroxides contained within the plasma samples, to produce a colored ferric-xylenol orange complex whose absorbance can be measured. The FOX2 reagent was prepared by dissolving ammonium ferrous sulphate (9.8 mg) in 250 mM H_2SO_4 (10 ml) to give a final concentration of 250 AM ferrous ion in acid. This solution was then added to 90 ml of HPLC-grade methanol containing 79.2 mg butylated hydroxytoluene (BHT). Finally, 7.6 mg xylenol orange was added with stirring to make the final working reagent (250 AM ammonium ferrous sulphate, 100 AM xylenol orange, 25 mM H_2SO_4, and 4 mM BHT in 90% vol/vol methanol in a final volume of 100 ml). The blank working reagent contained all components of the previous reagent except only ferrous sulphate. Aliquots (200 Al) of plasma were mixed with 1800 Al FOX2 reagent. After incubation at room temperature for 30 min, the vials were centrifuged at 5000 rpm for 10 min. Absorbance of the supernatant was then determined at 560 nm. Total peroxide content of plasma samples was determined as a function of the absorbance difference between test and blank tubes using a solution of H_2O_2 as standard. The coefficient of variation for individual plasma samples was less than 5%. Ratio of TOS to TAC was accepted as OSI[8].

Serum biochemistry (urea, creatinine, glucose, albumin, total cholesterol (TC), triglyceride (TG), low density lipoproteins (LDL), and high density lipoproteins (HDL), etc) were measured by using routine biochemical procedures on Aeroset/C8000 autoanalyzer (Abbott Diagnostics, Abbott Park, Chicago, IL, USA). Complete blood counts were measured on Cell-dyn 3700 (Abbott Diagnostics, Chicago, IL, USA). Intact parathormone (iPTH) was detected with two-site chemiluminescent enzyme-labeled immunometric method on IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum levels of C-Reactive Protein (C-RP), and ferritin were established by electrochemilüminescence method on Roche Elecsys 2010 immunoassay analyzer (Roche Diagnostics Corporation, Indianapolis, IN, USA). Clauss method was used to establish fibrinogen in citrated plasma on Beckman Coulter/IL Coagulation Systems (Instrumentation Laboratory, Brea, CA, USA). The same parameters were repeated after 3 months, and compared with the beginning of the study.

Statistical Analysis

Statistical analysis were done by student-*t* test, and wilcoxon signed rank test on SPSS-13.0 (SPSS Inc., Chicago, IL, USA) PC programme, data were shown as ± SD, and $p < 0.05$ was considered as satistically significant.

Results

Fiftytwo of the eligible 60 patients were completed the study, male female ratio was 21/31. Eight patients were excluded from study because of many reasons. Three of patients were transferred to different dialysis centers, 1 undergone to transplantation, 2 because of active tuberculosis, 1 because of Behcet's disease and 1 because of rheumatoid artritis. Among etiological causes hypertension (HT), chronic glomerulonephritis (CGN), and polycystic kidney disease (PCKD) were first three causes respectively. The mean age of dialysis was 45.9±41.5 months among patients. The etiology of ESRD detailed in Figure 1.

In comparing with controls it was seen that the systolic and the diastolic blood pressure were higher in patients (SBP: 157.5±44.2 vs 110.2±11.6 mmHg, DBP: 95.5±11.1 vs 75.2±8.0 mmHg, $p < 0.05$). In oxidative parameters there were statistical significance between patients and controls. Among patients, SH Groups: 0.22±0.01, TAC: 1.4±0.2, TOS: 9.5±4.5, OSI: 7.1±3.2, and those parametres were 0.36±0.04, 1.9±1.5, 6.2±3.2, and 3.2±1.1 respectively among controls ($p < 0.001$ for all). Demographic, clinical and hematological properties of patients and controls were compared in Table I.

In comparing with the beginning there was no statistically significance in biochemical parameters at the end of the 3 months. Comparison of biochemical and hematological parameters of patients before and after treatment were shown in Table II.

The inflammatory markers, C-RP, fibrinogen, and ferritin were significantly higher in patients than controls ($p = 0.017$, $p < 0.001$, and $p < 0.001$, respectively), and albumin was lower among patients ($p < 0.001$), (Table II). At the end of the study when we check those parameters again except albumin levels statistically significant decreasing was seen. C-RP was decrease to 6.3±9.2 from 9.7±7.5 mg/dl ($p = 0.045$), fibrinogen was decrease to 334.0±85.9 from 477.1±155.7 mg/dl ($p = 0.001$), and ferritin was decrease to 604.4±375.8 from 989.8±448.6 ng/dl ($p = 0.014$), (Table II).

At the end of the study, in comparing with the beginning the systolic blood pressure decreased to 121.5±24.4 from 157.5±44.2 mmHg, and the diastolic blood pressure to 80.4±10.3 from 95.5±11.1 mmHg ($p < 0.001$) (Figure 2).

At the end of the 3 months the TAC was increased to 1.7±0.4 from 1.4±0.2 μmol Trolox Eqv./L, and SH groups to 0.33±0.02 from 0.22±0.01 mmol/L, ($p < 0.001$) while TOS decreased to 7.2±1.1 from 9.5±4.5 μmol H_2O_2 Eqv./L, and OSI decreased to 5.0±0.8 from 7.1±3.2 ($p < 0.001$). The change in blood pressure, pro-oxidants, and anti-oxidants are detailed in Table III and Figures 2 and 3.

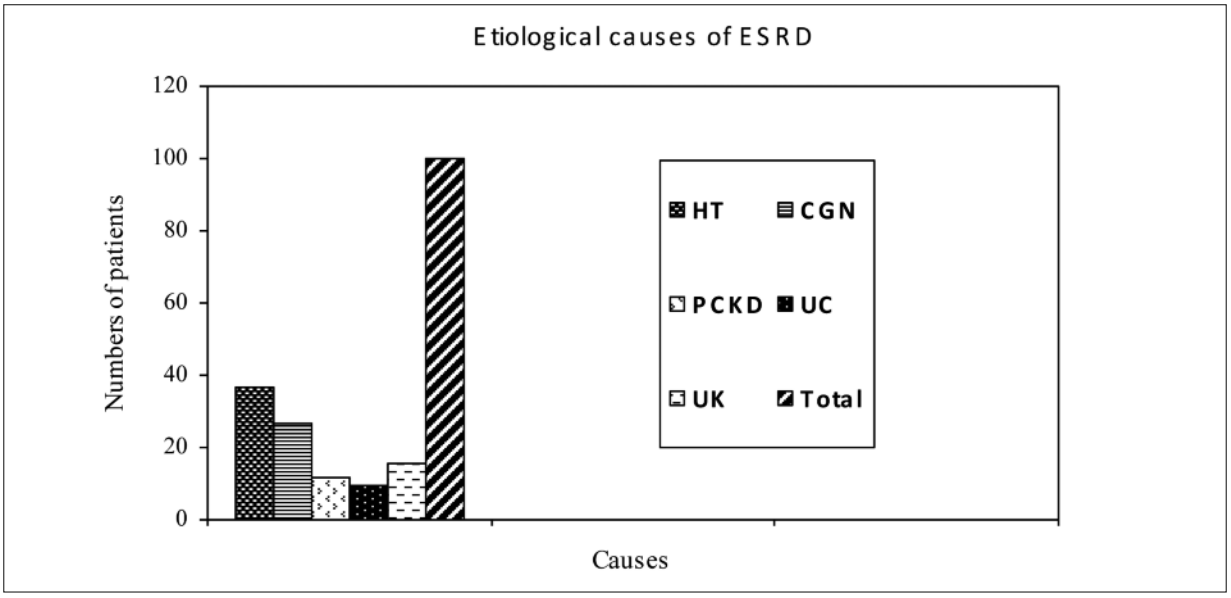

Figure 1. Etiological causes of ESRD among patients. HT: Hypertension; CGN: Chronic Glomerulonephritis; PCKD: Policystic Kidney Disease; UC: Urological Causes; UK: Unknown.

Table I. Demographic, clinical and hematological properties of patients and controls.

Parameters	Losartan group (n=52)	Control group (n=30)	p
Age (years)	38.9 ± 11.7	37.8 ± 10.5	0.568
Gender (M/F)	21/31	14/16	0.580
BMI (kg/m^2)	22.9 ± 4.2	23.5 ± 4.7	0.310
SBP (mmHg)	157.5 ± 44.2	110.2 ± 11.6	0.012
DBP (mmHg)	95.5 ± 11.1	75.2 ± 8.0	0.022
Glucose (mg/dl)	95.8 ± 22.8	90.1 ± 11.5	0.270
Na (mg/dl)	138.4 ± 3.5	139.9 ± 5.2	0.709
K (mg/dl)	5.3 ± 2.1	4.6 ± 0.7	0.044
Ca (mg/dl)	9.2 ± 1.1	9.1 ± 0.3	0.959
P (mg/dl)	5.6 ± 2.1	3.6 ± 0.4	< 0.001
Ca x P (mg^2/dl^2)	52.0 ± 8.8	32.9 ± 4.2	< 0.001
PTH (pg/ml)	312.8 ± 271.2	46.5 ± 17.1	< 0.001
Hgb (g/dl)	10.8 ± 1.7	14.2 ± 1.2	< 0.001
Ferritin (ng/ml)	989.8 ± 448.6	77.5 ± 54.4	< 0.001
Albumin (g/dl)	3.5 ± 0.6	4.4 ± 0.2	< 0.001
CRP (mg/dl)	9.7 ± 7.5	3.2 ± 0.4	0.012
Fibrinogen (mg/dl)	477.1 ± 155.7	212.9 ± 50.4	< 0.001
Uric acid (mg/dl)	8.9 ± 10.7	3.8 ± 1.6	0.043
Total cholesterol (mg/dl)	188.9 ± 77.3	161.7 ± 346.7	0.380
Triglyceride (mg/dl)	205.9 ± 83.5	145.1 ± 87.1	0.185
LDL-c (mg/dl)	107.9 ± 25.2	97.9 ± 22.2	0.388
HDL-c (mg/dl)	40.0 ± 13.9	45.9 ± 10.4	0.129

Table II. Comparison of Kt/V values, biochemical and hematological parameters of patients before and after treatment.

Parameters	Before treatment	After treatment	p
Kt/V	1.27 ± 1.01	1.26 ± 0.99	0.889
Glucose (mg/dl)	95.8 ± 22.8	96.8 ± 79.8	0.728
Na (mg/dl)	138.4 ± 3.5	139.2 ± 3.2	0.788
K (mg/dl)	5.3 ± 2.1	5.1 ± 0.8	0.512
Ca (mg/dl)	9.2 ± 1.1	9.1 ± 0.8	0.152
P (mg/dl)	5.6 ± 2.1	5.2 ± 1.7	0.134
Ca x P (mg2/dl2)	52.0 ± 8.8	50.7 ± 13.4	0.027
PTH (pg/ml)	312.8 ± 271.2	333.1 ± 215.7	0.124
Hgb (g/dl)	10.8 ± 1.7	10.9 ± 1.6	0.954
Ferritin (ng/ml)	989.8 ± 448.6	604.4 ± 375.8	0.006
Albumin (g/dl)	3.5 ± 0.6	3.5 ± 0.4	0.310
CRP (mg/dl)	9.7 ± 7.5	6.3 ± 9.2	0.036
Fibrinogen (mg/dl)	477.1 ± 155.7	334.0 ± 85.9	0.001
Uric acid (mg/dl)	8.9 ± 10.7	7.2 ± 1.3	0.418
Total cholesterol (mg/dl)	188.9 ± 77.3	188.5 ± 51.0	0.277
Triglyceride (mg/dl)	205.9 ± 83.5	195.4 ± 64.6	0.944
LDL-c (mg/dl)	107.9 ± 25.2	109.5 ± 27.2	0.446
HDL-c (mg/dl)	40.0 ± 13.9	44.6 ± 13.0	0.001

Table III. Comparison of systolic and diastolic blood pressure, pro-oxidants, and anti-oxidants of patients before and after treatment.

Parameters	Before treatment	After treatment	p
SBP[a]	157.5 ± 44.2	121.5 ± 24.4	< 0.001
DBP[a]	95.5 ± 11.1	80.4 ± 10.3	< 0.001
TAC[b]	1.4 ± 0.2	1.7 ± 0.4	< 0.001
TOS[c]	9.5 ± 4.5	7.2 ± 1.1	< 0.001
OSI	7.1 ± 3.2	5.0 ± 0.8	< 0.001
SH Groupsd	0.22 ± 0.01	0.33 ± 0.02	< 0.001

[a]mmHg; [b]µmol Trolox Eqv./L; [c]µmol H_2O_2 Eqv./L; [d]mmol/L.

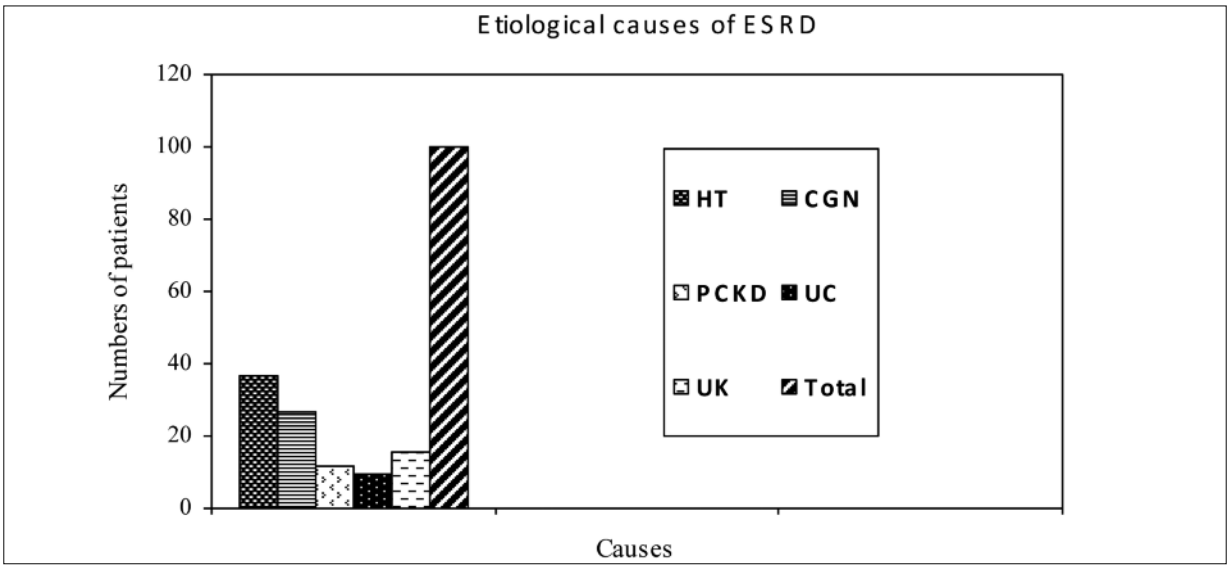

Figure 2. Change in BP with Losartan therapy. BT: Before Treatment; AT: After Treatment.

Discussion

Among ESRD patients, the balance between pro-oxidant and anti-oxidant capacity is shifted towards excess oxidative stress. Several deficiencies in different components of the anti-oxidant defence mechanisms such as reduced levels of vitamin C (due to dietary restriction in order to protect from hyperkalaemia, and losses during dialysis), reduced intracellular levels of vitamin E, reduced selenium concentrations and deficiency in the GSH scavenging system have been demonstrated[9,10]. Moreover, pro-oxidant activity is increased because of demographic characteristics of the patients suffering from ESRD, such as advanced age, diabetes mellitus, and hypertension, uremia, chronic infections and inflammatory status and factors associated with treatment. Also hemodialysis (HD) contributes to excess oxidative stres because of factors such as membrane bio-incompatibility, dialysis solutions and endotoxin challenge[11,12]. During HD, a direct increase in blood levels of ROS has been demonstrated[11].

Oxidative stress contributes to patients morbidity, and mortality. It is believed that oxidative stress promotes endothelial dysfunction and atherosclerosis and, therefore, cardiovascular complications. Among several qualitative changes in

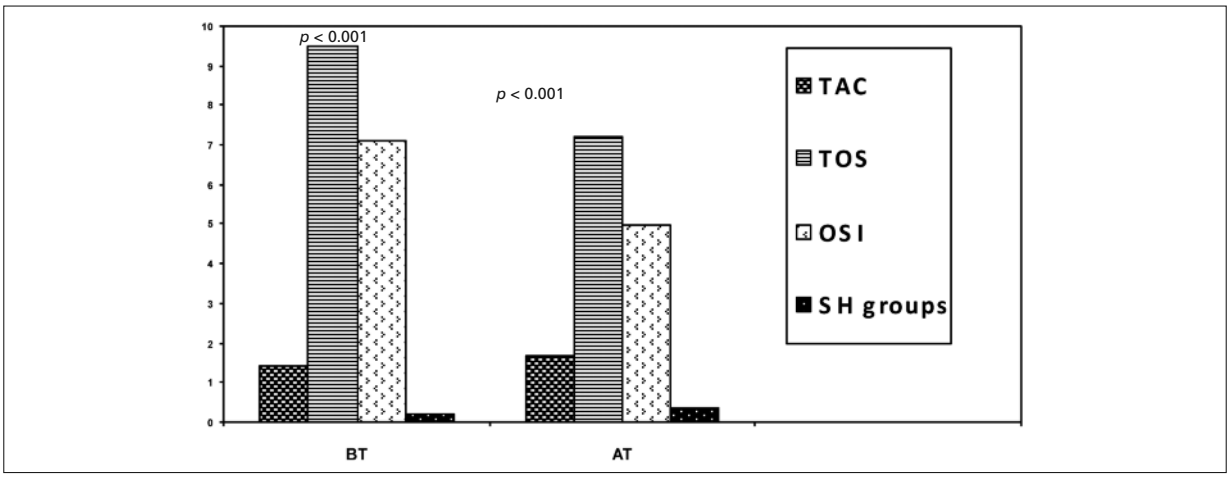

Figure 3. Comparison of pro-oxidants, and anti-oxidants of patients before (BT) and after treatment (AT). BT: Before treatment; AT: After treatment.

LDL among dialysis patients, increased levels of oxidized LDL and elevated titres of anti-oxidized LDL antibodies can be found[13]. Another possible mechanism may be an increase in oxidative stress and elicitation of inflammatory reactions induced by angiotensin II (Ang II)[5]. Indeed, inhibition of the renin–angiotensin system with ACEIs or ARBs in diabetes patients has now been well documented to decrease albuminuria and improve cardiovascular remodelling[14].

The relationship between malonyldialdehyde levels as an indicator of oxidative stress and the development of atherosclerosis was demonstrated recently in a cross-sectional study in dialysis patients[14]. Like these results, we found an increasing in levels of pro-oxidants, TOS and OSI, and a decrease in levels of anti-oxidants, TAC and SH groups among our patients. In comparing with age and gender matched controls, SH groups was 0.21±0.02, TAC: 1.3±0.3, TOS was 9.8±4.5, OSI was 7.6±3.6, among patients and those parametres were 0.33±0.05, 1.8±1.5, 6.5±3.2, and 3.6±1.5 respectively among controls ($p < 0.001$). These findings suggested us that once more, patients with ESRD are exposed to an excess of oxidative stress with a decreased antioxidant defence mechanism.

Nowaday, it is popular to research new thereupatic approaches for reducing oxidative stres, and CVE among ESRD patients. While antioxidants have not reduced CVE among general population, two clinical trials reported that use of antioxidants decrease morbidity and mortality in ESRD patients[9,10]. Angiotensin II (Ang II) has been shown to increase ROS levels in animal studies, via stimulation of NADPH oxidase activity[16,17], and human studies have supported these effects[17,18]. Ang II has also been implicated in upregulating the expression of the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) receptor, which is specific for oxidized LDL cholesterol. Inhibition of the generation of Ang II, whether by ACEI or ARB, should therefore attenuate these deleterious processes for organism**.** Onozato et al[19], showed that ACEI decreased proteinuria through inhibition of renal NADPH oxidase in rats with diabetic nephropathy, and like these results in their studies Fan et al[20], have shown that Candesartan, an ARB, decreased advanced glycosulated and products (AGEs) formation and oxidative stres in rats with diabetic nephropathies.

However, no prospective epidemiological studies are yet available to confirm a link between the extent of oxidative stress and patient's outcome among ESRD population ARBs and ACEIs are the most popular drugs preffered to correct this deleterious affects of excess oxidative stress. Nephroprotective effects of ACE inhibitors are well known, but the mechanisms underlying these favorable effects are not fully understood. These compounds also may have many metabolic actions in diabetic tissues, independent of their hemodynamic effects. ACE inhibitors have been shown to reduce lipid peroxidation in diabetic rat tissues[21], enhance antioxidant defenses in mouse tissues[22] and erythrocytes of type 2 diabetic patients[23]. As ACEIs, a new class of drugs, ARBs, also decrease albuminuria in diabetic patients[24,25]. As it was shown by our study, ARBs may be contribute these positive effects by improving oxidative stress among suffered population, especially ESRD patients.

Atherosclerosis is an inflammatory and a degenerative process, and traditional risk factors alone cannot explain the elevated prevalence of CVE and stroke in patients with ESRD. Non-tradititional risk factors, including activated complement, elevated such as C-RP acute phase reactans, and play an important role in the pro-atherosclerotic process. As increased oxidative stress and inflammation are both common features of ESRD, it has been speculated that there may be an association between them and endothelial dysfunction, contributing to an increased risk for CVE. Furthermore, oxidative stress may also stimulate an inflammatory response. Interestingly, several recent clinical studies suggest that oxidative stress and inflammation may be linked in ESRD patients. First, Nguyen-Khoa et al[26] observed that the presence of inflammation and the duration of dialysis are the most important determinants of oxidative stress in HD patients. Secondly, an association between F_2-isoprostanes and C-RP levels has been reported recently in HD patients[27]. Thirdly, in a study by Mezzano et al[28], in which 64 patients with advanced ESRD were studied, a significant positive correlation was found between acute phase proteins and markers of oxidative stress. Finally, it has been demonstrated that advanced oxidation protein products (AOPPs) act as mediators of oxidative stress and monocyte respiratory burst, which points to monocytes as both targets and actors in the immune dysregulation associated with ESRD[29]. Zhang et al[30] has shown that elevated leukocyte count and blood MPO levels are associated with the presence of coronary artery disease in a group of non-renal patients. Moreover,

a study has shown that a functional variant of the MPO gene is associated with cardiovascular disease in ESRD patients[31], and these results may support the link between inflammation, oxidative stress and endothelial dysfunction in ESRD patients. In this study our patients had higher levels of C-RP (vs), ferritin (vs), and fibrinogen (vs) supporting the elevated inflammation among patients with ESRD, and after treatment it was seen that the plasma levels of the markers of inflammation were reduced statistically by Losartan therapy. It was considered that Losartan may have beneficial affects on elevated inflammation among ESRD patients.

In recent study, when compared with the beginning of the study among all of patients, while the plasma levels of pro-oxidants, TOS and OSI, reduced ($p < 0.001$), the plasma levels of anti-oxidants, TAC and SH increased. Although their nephroprotective effects of ARBs were attributed to hemodynamic changes, the exact mechanism of action is not clear. Some reports indicate antioxidant effects of these drugs in non-diabetic rats[32,33], Tandon et al[34] showed that controlling HT improved oxidative stres in patients with HT. Among their patients while the levels of pro-oxidants, MDA, decreased with antihypertensive therapy, the levels of plasma superoxide dismutase increased. Our results agreed with Tandon et al findings. Among our patients there was a significant decrease in systolic and diastolic blood pressure, and a decrease in pro-oxidants, and an increase in anti-oxidants accompanied to this improvment in HT. Ogawa et al[14] suggested that the antioxidant effects of ARB were independent from antihypertensive effect. Whether controlling HT improves oxidative stress, or improving oxidative stress controls HT and it's complications, Losartan has benefical effects on oxidative status and controlling HT among ESRD patients. In this view, we thought that both of these two situations interacted with each other, and improved cardiovascuar complications, and elevated chronic microinflammatory status associated with oxidative stress among ESRD patients.

Conclusions

ESRD is a condition associated with increased, oxidative stress, reduced antioxidant status, and elevated microinflammation. Although having no control group for patients using Losartan limits the value of this study, we think that Losartan was an effective agent in controlling blood pressure, improving microinflammation, and oxidative stress through decreasing plasma levels of pro-oxidants and increasing anti-oxidants among non-diabetic ESRD patients, treated with hemodialysis. So ARBs may be a new therapeutic agent for improving oxidative stress, associated morbidity and mortality in this population.

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References

1) Luke RG. Chronic renal failure–a vasculopathic state. N Engl J Med 1998; 339: 841-843.
2) Locatelli F, Marcelli D, Conte F, D'Amico M, Del Vecchio L, Limido A, Malberti F, Spotti D. Cardiovascular disease in chronic renal failure: the challenge continues. Nephrol Dial Transplant 2000; 15(Suppl 5): S69-S80
3) Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? Am J Kidney Dis 1998; 32: 853-906
4) Brunner FP. Selwood NH on behalf of the EDTA Registry Committee. Profile of patients on RRT in Europe and death rates due to major causes of death groups. Kidney Int 1992; 42(Suppl 38): S4-S15.
5) Zoccali C. Cardiovascular risk in uraemic patients–is it fully explained by classical risk factors? Nephrol Dial Transplant 2000; 15: 454-457.
6) Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004; 37: 112-119.
7) Miyazawa T. Determination of phospholipids hydroperoxides in human blood plasma by a chemiluminescence's-HPLC assay. Free Radic Biol Med 1989; 7: 209-217.
8) Harma M, Harma M, Erel O. Increased oxidative stress in patients with hydatidiform mole. Swiss Med Wkly 2003; 133: 563-566.
9) Descamps-Latscha B, Drüeke T, Witko-Sarsat V. Dialysis-induced oxidative stress: biological aspects, clinical consequences, and therapy. Semin Dial 2001; 14: 193-199.

10) Canaud B, Cristol JP, Morena M, Leray-Moragues H, Bosc J, Vaussenat F. Imbalance of oxidants and antioxidants in haemodialysis patients. Blood Purif 1999; 17: 99-106.

11) Nguyen A, Lethias C, Zingraff J, Herbelin A, Naret C, Descamps-Latscha B. Hemodialysis membrane-induced activation of phagocyte oxidative metabolism detected in vivo and in vitro within microamounts of whole blood. Kidney Int 1985; 28: 158-167.

12) Descamps-Latscha B, Goldfarb B, Nguyen AT, Landais P, London G, Haeffner-Cavaillon N, Jacquof C, Herbelin A, Kazatchkine M. Establishing the relationship between complement activation and stimulation of phagocyte oxidative metabolism in hemodialyzed patients: a randomized prospective study. Nephron 1991; 59: 279-285.

13) Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome, Consensus Paper. Nephrol Dial Transplant 2003; 18: 1272-1280.

14) Ogawa S, Mori T, Nako K, Kato T, Takeuchi K, Ito S. Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. Hypertension 2006; 47: 699-705.

15) Boaz M, Matas Z, Biro A, Katzir Z, Green M, Fairnav M, Smetana S. Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis. Kidney Int 1999; 56:1978-1983.

16) Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension 2003; 42: 1075-1081.

17) Touyz RM. Reactive oxygen species and angiotensin II signaling in vascular cells – implications in cardiovascular disease. Braz J Med Biol Res 2004; 37: 1263-1273.

18) Touyz RM, Schiffrin EL. Ang II-stimulated superoxide production is mediated via phospholipase D in human vascular smooth muscle cells. Hypertension 1999; 34(4 Pt 2): 976-982.

19) Onozato ML, Tojo A, Goto A, Fujita T, Wilcox CS. Oxidative stress and nitric oxide synthase in rat diabetic nephropathy: effects of ACEI and ARB. Kidney Int 2002; 61: 186-194.

20) Fan Q, Liao J, Kobayashi M, Yamashita M, Gu L, Gohda T, Suzuki Y, Wang LN, Horikoshi S, Tomino Y. Candesartan reduced advanced glycation end-products accumulation and diminished nitro-oxidative stress in type 2 diabetic KK/Ta mice. Nephrol Dial Transplant 2004; 19: 3012-3020.

21) Kedziora-Karnatowska KZ, Luciak M, Poszkowski J. Lipid peroxidation and activities of antioxidant enzymes in the diabetic kidney: effect of treatment with angiotensin convertase inhibitors. IUBMB Life 2000; 49: 303-307.

22) De Cavanagh EM, Inserra F, Ferder L, Fraga CG. Enalapril and captopril enhance gluthatione-dependent antioxidant defenses in mouse tissues. Am J Physiol Regul Integr Comp Physiol 2000; 278: R572-R577.

23) Altuntas Y, Guven M, Ince E, Acbay O, Caner M, Kanigur-Sultuybek G. The in vitro effects of captopril on the levels of lipid peroxidation and gluthatione of erythrocytes in type II diabetes. J Basic Clin Physiol Pharmacol 1995; 6: 281-288.

24) Andersen S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockage in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000; 57: 601-606.

25) Lazano J, Liisterri JL, Aznar J, Redon J. Losartan reduces microalbuminuria in hypertensive microalbuminuric type 2 diabetics. Nephrol Dial Transplant 2001; 16(Suppl I): 85-89.

26) Nguyen-Khoa T, Massy ZA, De Bandt JP, Kebede M, Salama L, Lambrey G, Witko-Sarsat V, Drüeke TB, Lacour B, Thévenin M. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. Nephrol Dial Transplant 2001; 16: 335-340.

27) Handelman GJ, Walter MF, Adhikarla R, Gross J, Dallal GE, Levin NW, Blumberg JB. Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. Kidney Int 2001; 59: 1960-1966.

28) Mezzano D, Pais EO, Aranda E, Panes O, Downey P, Ortiz M, Tagle R, González F, Quiroga T, Caceres MS, Leighton F, Pereira J. Inflammation, not homocysteinemia, is related to oxidative stress and hemostatic and endothelial dysfunction in uremia. Kidney Int 2001; 60: 1844-1850.

29) Witko-Sarsat V, Friedlander M, Khoa TN, Capeillere-Blandin C, Nguyen AT, Canteloup S, Dayer JM, Jungers P, Drüeke T, Descamps-Latscha B. Advanced oxidation protein products as a novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol 1998; 161: 2524-2532.

30) Zhang R, Brennan M-L, Fu X, Aviles RJ, Pearce GL, Penn MS, Topol EJ, Sprecher DL, Hazen SL. Association between myeloperoxidase levels and risk of coronary artery disease. J Am Med Assoc 2001; 286: 2136-2142.

31) Pecoitys-Filho R, Stenvinkel P, Marchlewska A, Heimburger O, Barany P, Hoff CM Holmes CJ, Suliman M, Lindholm B, Schalling M, Nordfors L. A functional variant of the myeloperoxidase gene is associated with cardiovascular disease in end-stage renal disease patients. Kidney Int 2003; 84: S172-176.

32) Keidar S, Attias J, Smith J. The angiotensin II receptor antagonist losartan inhibits LDL lipid peroxidation and atherosclerosis in apolipoprotein E-deficient mice. Biochem Biophys Res Commun 1997; 236: 622-625.

33) Khaper N, Signal PK. Modulation of oxidative stress by a selective inhibition of angiotensin II type 1 receptor in MI rats. J Am Coll Cardiol 2001; 37: 1461-1466.

34) Tandon R, Sinha MK, Garg H, Khanna R, Khanna HD. Oxidative stress in patients with essential hypertension. Natl Med J India 2005; 18: 297-299.