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CLINICAL STUDY

Parameters of oxidative stress and echocardiographic indexes in patients on dialysis therapy

Hasan Kayabasi[1], Dede Sit[2], A. Engin Atay[3], Zulfukar Yilmaz[4], Ali Kemal Kadiroglu[1] and M. Emin Yilmaz[1]

[1] *Department of Nephrology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey*

[2] *Department of Nephrology, Fatih Government Hospital, Trabzon, Turkey*

[3] *Department of Internal Medicine, Silvan State Hospital, Diyarbakir, Turkey*

[4] *Department of Internal Medicine, Diyarbakir Government Hospital, Diyarbakir, Turkey*

ABSTRACT

Aim: Quantity of oxidative stress (OS) is enhanced in every stage of chronic renal failure (CRF). OS and its effects on echocardiographic indexes in patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) were evaluated. Materials and methods: Thirty-nine patients on CAPD, 32 patients on HD, and 30 healthy individuals with similar demographic features were included. Patients with diabetes mellitus and chronic inflammatory diseases were excluded. Blood samples were collected to examine hematological and biochemical parameters and levels of malonyldialdehyde (MDA), glutathione peroxidase (GSH-px), and superoxide dismutase (SOD) after a 12-hour fasting period in the middle of dialysis week. OS parameters were compared with ejection fraction (EF), interventricular septum diameter (IVSd), left ventricular posterior wall diameter (LVPWd), and left atrium diameter (LAd) determined in M-mod echocardiographic examination. Results: No significant difference was observed between MDA and GSH-px levels of patients and control group; however, SOD levels of patients group were significantly lower ($p < 0.0001$). SOD levels of patients on HD were lower than that of patients on CAPD ($p = 0.039$). Negative correlation was detected between MDA and EF ($r = -0.380$, $p = 0.001$); SOD has negative correlation with systolic blood pressure ($r = -0.265$, $p = 0.011$), diastolic blood pressure ($r = -0.230$, $p = 0.028$), phosphorus ($r = -0.327$, $p = 0.001$), intact parathyroid hormone (iPTH) ($r = -0.259$, $p = 0.013$), C-reactive protein (CRP) ($r = -0.235$, $p = 0.024$), fibrinogen ($r = -0.342$, $p = 0.001$), and total cholesterol ($r = -0.249$, $p = 0.017$); and positive correlation with hemoglobin ($r = 0.414$, $p < 0.001$) and albumin ($r = 0.367$, $p < 0.001$). MDA was independently related with age ($\beta = -0.258$, $p = 0.035$), male gender ($\beta = -0.312$, $p = 0.004$), and EF ($\beta = -0.461$, $p < 0.001$). No correlation was determined between antioxidants and cardiac indexes. Conclusion: SOD levels decreased significantly especially in patients on HD, and it was observed that lower levels of SOD would lead to OS in patients on HD and CAPD when compared to healthy individuals; MDA levels were independently influenced from EF.

Keywords: dialysis; oxidative stress; echocardiographic indexes

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Correspondence: Dr. Hasan Kayabasi, Department of Nephrology, Faculty of Medicine in Dicle University, 21100 Diyarbakir, Turkey; tel: +904122488001/4786, +905072336438; Fax: +90 412 248 81 71; E-mail: drkayabasi@yahoo.com

INTRODUCTION

Atherosclerosis and associated cardiovascular diseases (CVD) are the most common causes of mortality and morbidity in end-stage renal disease (ESRD).[1] Risk of CVD is 3.5–50 times higher in patients undergoing renal replacement therapy than in general population.[2,3] Augmentation in the risk of CVD in patients with ESRD is not only related to traditional risk factors, even when the traditional risk factors are fixed, but also related to untraditional and uremia-specific risk factors such as hypertension secondary to chronic hypervolemia, anemia, disorders of calcium–phosphorus (Ca–P) metabolism, hypercatabolism, hyperhomocysteinemia, and chronic microinflammation subsequent to oxidative stress (OS).[4]

OS is described as dominance of pro-oxidants to antioxidant systems and plays an important role in the development of systemic diseases and related complications.[5,6] It was concluded that proinflammatory cytokines and OS are cardinal factors for atherosclerosis in uremic patients. In patients with ESRD, OS is enhanced because of increased lipid peroxidation and decreased antioxidant activity that reflects basic properties of oxidative damage.[7]

Several studies mentioning the relation of ESRD and OS have been carried out; however, few studies

examined the relation between OS and dialysis modalities and its effects on echocardiographic indexes of left ventricular hypertrophy.

In this study we aimed to evaluate the relation between OS and dialysis modalities and its effects on echocardiographic parameters such as ejection fraction (EF), interventricular septum diameter (IVSd), left ventricular posterior wall diameter (LVPWd), and left atrium diameter (LAd) in patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD).

MATERIALS AND METHODS

Thirty-nine patients on CAPD and 32 patients on HD followed up for at least 6 months period in the Dialysis Center of Medical School, Dicle University, and age-matched 30 healthy individuals were included into the study. The study was planned as a cross-sectional study and carried out in two stages. In the first stage, the patients and control groups were constituted. Parameters of biochemistry and OS were examined in both groups. In the second stage, the patients were divided into subgroups according to dialysis modality: HD (Group 1) and peritoneal dialysis (Group 2). Blood pressure of patients was measured after a period of 15 min resting and before dialysis in HD patients and after 15 min resting among CAPD patients. Clinical, hematological, biochemical examination, and the parameters of OS were evaluated and the effects of OS on echocardiographic indexes were determined. Patients with diabetes mellitus, chronic infection, or inflammation status (such as tuberculosis, rheumatoid arthritis, and amyloidosis), ischemic heart disease, congestive heart failure, who were hypertensive and were on antihypertensive therapy, and who refused to participate in the study were excluded. Written informed consent had been taken from all patients.

Collection of blood samples

Blood samples were collected from antecubital vein subsequent to a 12-hour fasting period before dialysis therapy in patients on HD and first removal in the morning among patients on CAPD. A pair of sterile biochemistry tubes including no additives, for parameters of OS and biochemical analysis and a hemogram tube including K-EDTA for erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) examination, were prepared. Samples were centrifuged in 3000 turn for 15 min in room temperature. Serum samples and erythrocyte packages were collected in Eppendorf tubes and stored in −80°C to examine parameters of OS. Malonyldialdehyde (MDA), SOD, and GSH-Px analyses were studied in Biochemical Laboratory of Medical School in Harran University. Routine biochemical analysis was carried out in Central Laboratory of Medical School in Dicle University.

Malonyldialdehyde

Samples were stored in −80°C to examine plasma levels of MDA. Briefly, 50 μL of plasma was added to 1 mL of 10 mmol/L diethylthiobarbituric acid (DETBA) reagent in phosphate buffer (0.1 mol/L, pH 3). The mixture was mixed for 5 s and incubated for 60 min at 95°C. Samples were placed in ice for 5 min and then added to 5 mL of butanol. The mixture was shaken for 1 min to extract the DETBA–MDA adduct and then centrifuged at 1500 × *g* for 10 min at 4°C. Fluorescence of the butanol extract was measured at excitation wavelength of 539 and emission wavelength of 553. 1,1,3,3-Tetraethoxypropane (Sigma-Aldrich®, St. Louis, MO, USA) was used as a standard solution, and the values were presented as μmol/L.[8,9]

Erythrocyte superoxide dismutase activity

Erythrocyte levels of SOD were measured spectrophotometrically using Randox Lab. Ransod® (No. SD 125 Randox Laboratories, Diamond Road, Crumlin, UK) trademark kit.[10]

Glutathione peroxidase

Levels of GSH-px were measured by modified method of Paglia Valentine enzymatic-UV using Ransel kit (catalog no: RS 504; Randox Laboratories) spectrophotometrically.[11]

Echocardiographic analysis

Echocardiographic indexes were assessed using Hewlett–Packard Sonos 4500® Echocardiography (Philips, Andover, MA, USA) system transthoracically. Echocardiographic examination was instituted in two-dimensional M-mod, C-Doppler echocardiography in left lateral decubitus position, and in the assistance of parasternal long–short axis, apically four-space and five-space view. According to the recommendations of American Echocardiography Association, entire echocardiographic examination was done by the same physician in the middle of the day to prevent circadian changes. Measurements of EF, IVSd, LVPWd, and LAd were instituted in M-mod echocardiographic examination subsequent to dialysis period.

Statistical analysis

Statistical analysis was carried out using SPSS 13.0 PC program. Independent variables and dependent variables were determined by Student's *t*-test and linear regression methods, respectively, and the relation of variables was determined by Pearson's correlation. A p-value < 0.05 was accepted as significant, and data were shown as ±SD.

RESULTS

Patients on HD (n = 32), CAPD (n = 39), and healthy controls (n = 30) – totally 101 individuals – were included in the study. Demographic, clinical, and biochemical properties of patients and control group were compared and shown in Table 1.

No significant difference was observed between patients and control group in age, sex, levels of glucose, Na, Ca, total cholesterol, triglyceride, and low-density lipoprotein (LDL)-c; however, there was significant difference between other parameters.

Patients were divided into two subgroups as HD and CAPD, and demographic, clinical features and laboratory examination were compared as shown in Table 1.

Between subgroups (HD and CAPD patients), no significant difference was observed in age, sex, BMI, blood pressure, Na, hemoglobin, ferritin, Ca, parathyroid hormone (PTH), C-reactive protein (CRP), and triglyceride levels. Kt/V values were 1.46 ± 0.15 among HD patients and 2.13 ± 0.09 among CAPD patients. Although serum levels of phosphorus (p = 0.002), Ca × P (p = 0.036), albumin (p = 0.009), and high-density lipoprotein (HDL)-c (p < 0.001) were significantly higher in patients on HD, serum levels of glucose (p = 0.010), potassium (p = 0.002), total cholesterol (p = 0.012), and LDL-c (p = 0.020) were significantly higher in patients on CAPD.

Although there was no significant difference between patients and control groups in the levels of MDA as pro-oxidant and GSH-px as antioxidant (p = 0.202 vs. p = 0.456), erythrocyte SOD levels were significantly different between groups (p < 0.001) (Figure 1). OS parameters between patients and controls were compared in Table 2.

Among subgroups of patients according to dialysis modality, there was no significant difference between MDA (p = 0.224) and GSH-px (p = 0.425) levels. Significant difference was determined in SOD levels (p = 0.039). According to the OS effects of pro-oxidant (MDA) and antioxidant (GSH-px), results were relatively better in patients on CAPD than patients on HD, even it was insignificant as shown in Table 3 and Figures 2–4.

No statistical significance was found between GSH-px and SOD levels when OS parameters and

TABLE 1. Demographic clinical and biochemical properties of patients and control group.

Parameter	Patients group (n = 71)	Control group (n = 30)	P	CAPD (n = 39)	HD (n = 32)	p
Age (years)	40.9 ± 14.0	38.0 ± 10.5	0.389	38.9 ± 13.0	43.4 ± 15.0	0.183
Sex (M/F)	34/37	14/16	0.983	17/22	17/15	0.424
BMI (kg/m^2)	21.9 ± 4.3	24.3 ± 3.7	0.025	22.3 ± 3.8	21.4 ± 4.9	0.386
SBP (mmHg)	136.6 ± 28.2	116.6 ± 12.3	0.002	136.6 ± 32.1	136.5 ± 23.0	0.988
DBP (mmHg)	83.9 ± 13.6	77.1 ± 9.0	0.035	85.6 ± 13.7	81.8 ± 13.5	0.251
Glucose (mg/dL)	104.3 ± 49.9	93.1 ± 11.8	0.314	118.6 ± 62.7	87.7 ± 17.1	0.010
Na (mEq/L)	139.5 ± 3.5	139.8 ± 2.2	0.791	139.2 ± 3.6	139.9 ± 3.4	0.419
K (mEq/L)	4.8 ± 1.0	4.1 ± 0.2	0.003	4.5 ± 0.9	5.1 ± 1.0	0.014
Ca (mg/dL)	9.3 ± 1.2	9.3 ± 0.3	0.901	9.5 ± 1.2	9.1 ± 1.1	0.108
P (mg/dL)	5.9 ± 2.0	3.7 ± 0.5	<0.001	5.2 ± 1.6	6.7 ± 2.0	0.002
Ca × P (mg^2/dL^2)	55.2 ± 19.2	34.9 ± 4.9	<0.001	50.9 ± 20.1	60.5 ± 16.9	0.036
iPTH (pg/mL)	382.6 ± 386.9	49.5 ± 19.1	<0.001	383.9 ± 75.5	380.9 ± 45.0	0.974
Hemoglobin (g/dL)	10.4 ± 1.7	14.4 ± 1.2	<0.001	10.6 ± 1.9	10.2 ± 1.4	0.387
Ferritin (ng/mL)	1157.2 ± 1641.7	100.5 ± 104.4	0.004	999.9 ± 630.8	1349.0 ± 2351.4	0.377
Albumin (g/dL)	3.3 ± 0.5	4.3 ± 0.2	<0.001	3.1 ± 0.6	3.5 ± 0.5	0.009
CRP (mg/dL)	13.5 ± 29.4	3.4 ± 0.4	0.119	14.6 ± 5.2	12.2 ± 4.4	0.735
Fibrinogen (mg/dL)	516.7 ± 166.7	250.9 ± 52.4	<0.001	587.0 ± 174.9	442.0 ± 121.6	0.0001
T.Cholesterol (mg/dL)	185.6 ± 56.6	171.7 ± 36.7	0.292	200.7 ± 61.1	167.2 ± 44.4	0.012
Triglyceride (mg/dL)	185.8 ± 139.4	140.1 ± 97.1	0.164	186.1 ± 27.1	185.5 ± 16.4	0.986
LDL-C (mg/dL)	111.9 ± 38.1	97.9 ± 29.2	0.126	121.3 ± 37.5	100.3 ± 36.3	0.020
HDL-C (mg/dL)	38.6 ± 12.0	45.9 ± 10.4	0.014	43.9 ± 12.7	32.1 ± 6.9	<0.001

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

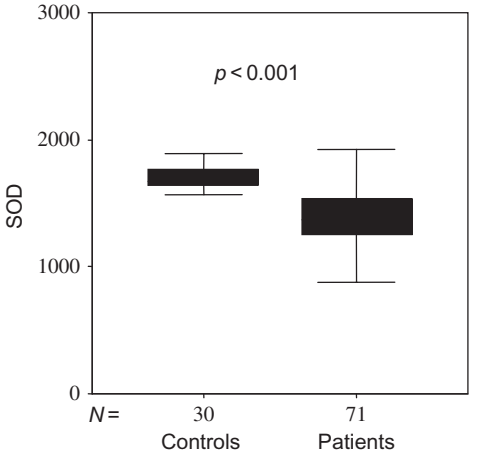

FIGURE 1. Comparison of SOD levels between dialysis patients and control group.

TABLE 2. Parameters of pro-oxidant and antioxidants between patients and controls.

Parameters	Patient group (n = 71)	Control group (n = 30)	p
MDA (µmol/L)	5.9 ± 2.4	5.1 ± 1.8	0.202
GSH-px (U/dL)	65.5 ± 3.4	71.0 ± 28.6	0.456
SOD (U/gHb)	1391.6 ± 252.9	1730.4 ± 228.4	<0.001

TABLE 3. Oxidative stress and echocardiographic data.

Parametrial	HD (n = 32)	CAPD (n = 39)	p
MDA	6.2 ± 2.8	5.5 ± 1.9	0.224
GSH-px	63.7 ± 8.0	68.0 ± 41.8	0.425
SOD	1589.7 ± 274.0	1366.8 ± 234.8	0.039
EF	63.1 ± 6.5	62.0 ± 3.3	0.373
IVSd	1.18 ± 0.18	1.20 ± 0.22	0.718
LVPWd	1.33 ± 0.20	1.18 ± 0.22	0.378
LAd	3.3 ± 0.5	3.4 ± 0.5	0.492

echocardiographic indexes were taken into account. There was a negative correlation between MDA levels and EF (r = –0.380, p = 0.001). Also negative correlations were determined between SOD and systolic blood pressure (r = –0.265, p = 0.011), diastolic blood pressure (r = –0.230, p = 0.028), biochemical parameters such as p (r = –0.327, p = 0.001), PTH (r = –0.259, p = 0.013), CRP (r = –0.235, p = 0.024), fibrinogen (r = –0.342, p = 0.001), total cholesterol (r = –0.249, p = 0.017). Results were detailed in Table 4. Positive correlation was determined between SOD and

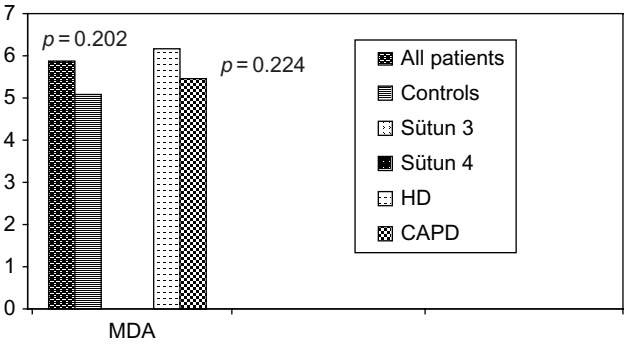

FIGURE 2. Comparison of malondialdehyde levels between HD, CAPD, and control groups.

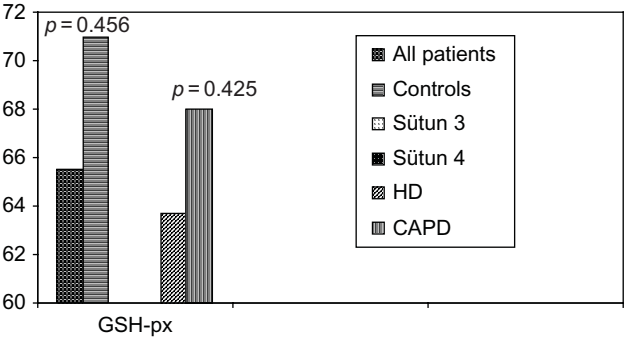

FIGURE 3. Comparison of glutathione peroxidase levels between HD, CAPD, and control groups.

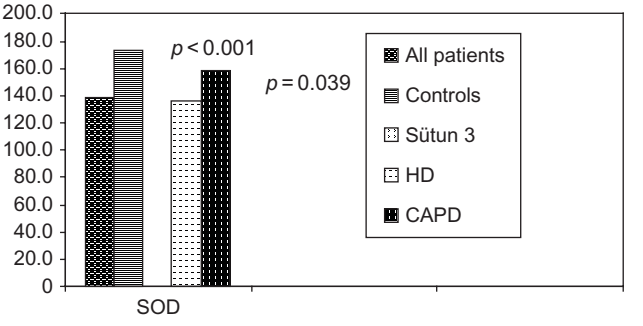

FIGURE 4. Comparison of superoxide dismutase levels between patients on HD, SAPD, and control groups.

hemoglobin (r = 0.414, p < 0.001) or albumin (r = 0.367, p < 0.001).

MDA was independently correlated with age (β = –0.258, p = 0.035) and male gender (β = –0.312, p = 0.004) (Figure 5). MDA was the only antioxidant or pro-oxidant parameters that has significant correlation with echocardiographic indexes, especially with EF (β = –0.461, p < 0.001). No correlation was

TABLE 4. Results of Pearson's correlation.

	r	*p*
MDA & EF	–0.380	0.001
SOD & SKB	–0.265	0.011
SOD & DKB	–0.230	0.028
SOD & P	–0.327	0.001
SOD & PTH	–0.259	0.013
SOD & CRP	–0.235	0.024
SOD & Fibrinojen	–0.342	0.001
SOD & T. Kolesterol	–0.249	0.017

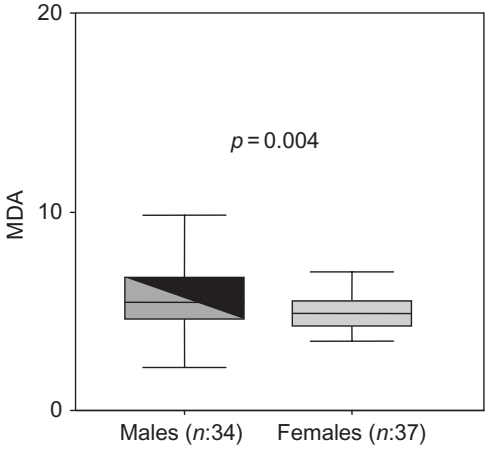

FIGURE 5. MDA levels of male and female patients.

detected between antioxidants (GSH-px or SOD) and cardiac parameters.

Linear regression analysis pointed out positive correlation between MDA, as dependent variable, and echocardiographic indexes like EF, LAd, IVSd versus LVPWd (r = 0.189 and p = 0.007), as independent variables. Other OS parameters and echocardiographic indexes have no significant correlation.

DISCUSSION

ESRD is usually collaborated with premature atherosclerosis. This is generally committed to nontraditional risk factors such as hypervolemia, anemia, Ca–P metabolism disorders, hyperhomocysteinemia, and chronic inflammation besides traditional risk factors.[12] Recently, role of OS as a nontraditional risk factor is prominent. Association of OS and carotid artery intima-media thickness accepted as earlier predictor of atherosclerosis,[12,13] related to OS and CRP that is an independent risk factor of atherosclerotic heart disease, and oxide-LDL cholesterol deposition in foam cells that forms atheromatous plaque are the factors suggesting the role of OS in atherosclerotic process.

OS is a process resulting in tissue damage subsequent to the elevation of pro-oxidants and the reduction of antioxidant or both that is physiologically balanced.[14] ESRD is a disorder associated with OS that is not totally enlightened. Possibly, OS has a multifactorial origin in ESRD. Quantity of OS is enhanced because of inadequate clearance of OS substances, use of bioincompatible membranes, dialysate reactions, reduced production of antioxidants, HD itself that is a model for OS, and iron replacement that would precipitate OS.

Elevated quantity of OS is attributed to lipid peroxidation, endothelial dysfunction, and increased modification of proteins. Elevated levels of MDA reflects elevated lipid peroxidation[15] as a marker of enhanced OS. In recent study there was no statistical significance between patients undergoing HD and CAPD (p = 0.224).

GSH-px, an enzyme which has antioxidant effect, is secreted from proximal tubule cells and erythrocytes, plays a critical role in antioxidant defense system of plasma.[16] Insignificant reduction levels of GSH-px were determined in patients on HD when compared with control group (p = 0.456) and in patients on CAPD when compared with HD (p = 0.425). Although contradictious results are present, most of other studies support our data.[17–20]

Erythrocytes SOD levels, a parameter of antioxidant defense system, was significantly lower in patients on dialysis therapy than control group and in patients on HD than CAPD ($p < 0.001$ and p = 0.039, respectively). Statistically no significant difference was observed in levels of GSH-px between patients and control group and between patients on HD and CAPD. Similar results were observed in some other reports.[21] It is associated with adequacy of dialysis (Kt/V = 1.68), acceptable levels of anemia, secondary hyperparathyroidism, and parameters of nutrition such as albumin and cholesterol. Many studies reflecting similar results are present.[22–26]

Antioxidant defense systems are less affected in patients on peritoneal dialysis than HD.[15–17] This is related to less frequent presence of anemia and moderate amount of lipid peroxidation.[23] Similarly, levels of SOD enzyme were significantly lower in patients on CAPD than HD. Parameters of antioxidant defense system were better in patients on CAPD according to extracorporeal circulation and elevated activation of immune system in patients on HD. This is attributed to the adequacy of dialysis and better results of other related parameters in patients on CAPD as it was same as HD. OS is a higher potential risk factor for patients on HD; however, it was also elevated in patients on CAPD. Elevation occurs independently from therapy

in uremic patients as it was supported by many other reports.[12,16,27]

Negative correlation between SOD and biochemical parameters like P, PTH, CRP, fibrinogen, and total cholesterol and positive correlation between hemoglobin ($r = 0.414$, $p < 0.001$) and albumin ($r = 0.367$, $p > 0.0019$) were determined. Relation between OS parameters and both CRP, as an inflammation marker, or secondary hyperparathyroidism and nutritional factors, indicate not only elevation of prooxidants but also synchronous insufficiency of antioxidant defense systems. Several studies supporting this data are observed in the literature.[28]

Chronic renal failure (CRF) is common due to frequent association of hypertension and etiological factors including diabetes mellitus, chronic glomerulonephritis, polycystic kidney disease, or left ventricular hypertrophy both secondary to hypertension or subsequent to anemia, secondary hyperparathyroidism, and activation of renin–angiotensin–aldosterone system.[29] Several studies pointed out the association of LVH and stroke, acute coronary syndromes, heart failure, and sudden death. LVH is an independent risk factor for increased incidence of CVD besides coronary artery disease, heart failure, stroke, and mortality secondary to both cardiac and noncardiac causes in male and female patients. LVH is described according to the relation of mass of left ventricle and relative wall thickness. Echocardiography is the most common diagnostic procedure. Increase of left ventricular mass in hypertensive patients has predictive value and better predictor of cardiac complication.[30,31] OS is related with cardiovascular damage in earlier and late stages of CRF in both adults and pediatric population.[27,32] In our study, no statistical significance was observed between echocardiographic indexes and plasma GSH-px; however, negative correlation between MDA and EF ($r = -0.380$, $p < 0.001$) or between SOD and systolic-diastolic blood pressure suggests particular role of OS on left ventricle hypertrophy. Positive relation of MDA, as an independent variable, and echocardiographic indexes like EF, LAd, IVSd, and LVPWd, as a dependent variable ($r = 0.189$ and $p = 0.007$) supports our data in linear regression analysis. We suggest that favorable results are related to adequate dialysis therapy for more than 6 months and better control of anemia, hypervolemia, inflammation, nutritional status, Ca–P metabolism, dyslipidemia, and hypertension.

In conclusion, SOD levels diminished and caused OS in ESRD patients on CAPD and particularly HD according to control group. MDA levels independently correlates with age, male gender, and EF, and finally SOD levels have negative correlation with blood pressure, P, PTH, CRP, fibrinogen, and positive correlation with hemoglobin and albumin.

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