Paraoxonase 1 is Independently Associated with Pulmonary Pulse Transit Time at Hemodialysis Patients

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Abstract

Objectives

Pulmonary hypertension (PH) and fibrosis are important complications of hemodialysis patients. There is a direct relationship between oxidative stress and PH. Pulmonary pulse transit time (pPTT) is a valuable parameter for determining PH and fibrosis. Paraoxonases (PON1) are potent antioxidant and anti-inflammatory enzymes. At this study we aimed to determine relationship between PON1 and echocardiography parameters at hemodialysis patients.

Methods

36 patients on maintenance hemodialysis for at least 3 months are enrolled to the study. Blood samples and echocardiography measurements were taken before and after hemodialysis session.

Results

The mean age is 59,3 ± 13,27 years. Mean hemodialysis duration is 6,2 ± 5,5 years. Post hemodialysis PON1 was higher than pre hemodialysis PON1 ($r = 0.967$, $p < 0.0001$). Post hemodialysis PON1 and post hemodialysis pPTT were negatively correlated ($r=-0.410$, $p = 0.009$). Pre hemodialysis PON1 and pre hemodialysis pPTT measurements were negatively correlated ($r=-0.381$, $p = 0.014$). Post hemodialysis PON1 and post hemodialysis E' were positively correlated ($r = 0.345$, $p = 0.050$). Multiple linear regression analysis was run to predict PON1 from pPTT, creatinine, CRP and PTH, the model predicted relation $p < 0,05$, $R = 0,527$, pPTT ($p < 0,05$) added statistically significant to the prediction and CRP ($p = 0,055$) is close to statistical significance.

Conclusion

Our study showed first time at the literature that there is an independent correlation between pPTT, an indicator for PH and pulmonary fibrosis, and PON1.

Introduction

End stage renal disease (ESRD) patients have 10 times higher risk for developing cardiovascular disease (CVD) compared to control groups (1). It has been suggested that oxidative stress and inflammation are important contributors at pathophysiological process of development of CVD at HD patients recent years (1, 2, 3, 4).

Chronic Kidney Disease (CKD) is characterized with increased oxidative stress (OS), chronic inflammation and endothelial dysfunction which entails progression of kidney injury and systemic complications of

CKD including especially CVD (4). Oxidative stress is more severe at ESRD patients receiving maintenance HD in particular (5). OS is also found increased in early stages of CKD (6). OS increase at CKD occurs by disruption of the balance between oxidative products and antioxidant defense mechanisms which includes upregulation and activation of enzymatic pathways such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, lipoxygenase, uncoupled nitric oxide synthase (NOS) and the mitochondrial respiratory chain resulting production of oxidative molecules reactive oxygen species (ROS) and nitrogen species, such as nitric oxide (NO)(1, 4, 5, 7). Antioxidant enzymes mainly composed of superoxide dismutase (SOD), catalase, selenium-containing glutathione peroxidase become insufficient against oxidative stress burden (4). OS begets activation of inflammatory mediators and triggers oxidation and modification of nucleic acids, proteins, lipids, carbohydrates hence leading to lipid peroxidation and the accumulation of advanced glycation end products (AGEs) which cause tissue damage in CKD. Also, hemodialysis itself is defined with increased oxidative stress, resulting from antioxidant depletion during dialysis procedure and accumulation of oxidative molecules (4, 5, 7).

Enhanced OS and inflammation which causing accumulation of oxidative products such are ROS and NO are triggered by hemodialysis are major contributors for development of endothelial dysfunction, vascular calcification, progression of atherosclerosis and resulting CVD. Systolic and diastolic function is worsened by ROS mediated cellular signaling and gene expression. Cardiac remodeling which features myocardial apoptosis, intramyocardial fibrosis, impaired diastolic filling, contractile dysfunction and chamber dilation are linked with oxidative stress which its processes mediated by the activation of several promitogenic kinases, transcription factors, matrix metalloproteinases and fibroblast proliferation (1).

Paraoxonases (PON) including PON1, PON2, and PON3 are potent antioxidant and anti-inflammatory enzymes (8). PON1 is an esterase/lactonase glycoprotein synthesized in the liver and found mainly in high-density lipoproteins (HDLs) at circulation which derives its name from its ability to hydrolyze paraoxon, a pesticide component (8, 9). PON-2 and PON-3 have lactonase activity but no paraoxonase or arylesterase activity. PON1 has wide range of abilities encompassing to hydrolyze arylesterases such as, phenyl acetates and hydrolyze lactones such as homocysteine thiolactone which is a component of atherosclerosis pathogenesis (1, 9). PON1 plays an important role at anti oxidative activity of HDL (10). HDL contains PON1 in addition to its protein and lipid components (11). Degradation of hydrogen peroxide and lipid peroxides, prevention of lipoprotein oxidation, reverse cholesterol transport which includes efflux of cholesterol from macrophages, prevention of foam cell formation is some of the effects which PON1 linked with HDL (1, 5). Decrease of PON1 activity is related with atherosclerosis which can be the possible cause of CVD at HD patients (11).

Pulmonary hypertension (PH) and pulmonary fibrosis (PF) are clinically important complications of HD patients.PH and pulmonary fibrosis are reported to have high prevalence at HD patients and pathogenesis of the both have direct links to oxidative stress and inflammation (12, 13, 14).PH and PF are related with worse outcomes and independently associated with increased CVD risk at HD patients (15). Importance of early and correct diagnosis of PH and PF is essential because of its tendency to asymptomatic course

until end stage and HD patients commonly have edema and dyspnea related to volume overload which makes PH diagnosis difficult (14). Accumulation of OS products, ROS activation, endothelial dysfunction, NO decrease, increase at the levels of fibrin storages and endothelin, hemodynamic effects of the arteriovenous fistula and grafts, neutrophil activation related to dialysis membrane, pulmonary vascular calcification and extensive growth of endothelial cells are among the causes for PH. Increase of growth factors such as TGF beta, PDGF, FGF, pulmonary angiotensin converting enzyme activation, cytokine activation together with pulmonary circulation impairment and chronic volume overload helps to smooth muscle cell proliferation and pulmonary fibrosis at hemodialysis patients (12, 13, 16). Gold standard for PH diagnosis is right heart catheterization which is poorly accessible and invasive procedure (17). Pulmonary pulse transit time (pPTT) is a noninvasive method which is a valuable parameter for determining PH and PF (18).

At this study we aimed to determine relationship between PON1 activity and echocardiography parameters early diastolic mitral annular velocity (E'), pulmonary artery pressure (PAP), tricuspid annular peak systolic excursion (TAPSE), myocardial performance index (MPI), ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) (E/A ratio), posterior wall thickness (PWT), interventricular septum thickness (IVS), left atrium diameter (LA), ejection fraction (EF) and pulmonary pulse transit time before and after HD session at ESRD patients. We investigated relation between PON1 and echocardiography parameters for pulmonary fibrosis parameters.

Material And Methods

Thirty-six patients with ESRD on maintenance HD for at least 3 months are enrolled to the study. All patients undergo three, 4-hour HD session per week. Designated exclusion criterias are malignancy, sepsis, connective tissue or other inflammatory disorders and hepatic insufficiency. Study was performed according to the requirements of the Ahi Evran University Faculty of Medicine Research Ethics Committee (Resolution No: 2020-19/135, 22/12/2020) and written informed consent to participate at this study have taken from all participants. The procedures followed were in accord with the Declaration of Helsinki. All patients in the study underwent a detailed medical history and clinical examination. Demographic and clinical characteristics, including age, gender, smoking habit and duration of HD were recorded.

A fasting blood sample pre-HD and post-HD blood sample at the end of the dialysis session were taken from all of the patients. All patients underwent echocardiography before hemodialysis and after hemodialysis session by expert cardiologist. Pulmonary vein flow was examined by pulse wave Doppler of the right superior pulmonary vein from the apical four-chamber view. Pulmonary pulse transit time is determined as the time interval between the R wave in the electrocardiography (ECG) and the corresponding peak late systolic pulmonary vein flow velocity which calculated with two separate pulse wave doppler evaluation during the same echocardiography examination. Doppler measurements and documentations were made with a concurrent superimposed ECG.

PON1 activity measurement pre HD and post HD done using paraoxonase assay kit. Venous blood samples were taken from the antecubital vein and transported to routine biochemistry tubes and tubes containing K2EDTA. Biochemistry tubes were centrifuged at 3000 rpm for 10 minutes after waiting for 30 minutes for clotting. Serums are divided into aliquots. Complete blood and routine biochemistry parameters were measured immediately. Serums separated into aliquots were stored at -80 degrees until analysis of serum PON activities. Complete blood count (CBC) was measured on the auto-analyzer (Sysmex XN-1000, Sysmex Company, Japanese). Routine serum biochemical parameters were measured on a routine biochemistry auto-analyzer (Cobas 8000, Roche Diagnostic Corp., Mannheim, Germany).PON activities was measured by spectrofotometric commercial kits (Relassay, Gaziantep, Turkey) in Cobas C 501 autoanalyser (Roche Diagnostics, Mannheim, Germany). PON-1 activity was determined using paraoxon as a substrate in the presence of sodium choride (salt stimulated activity). The rate of paraoxon hydrolysis (diethyl-p-nitrophenyl phosphate) was measured by monitoring the increase in absorbance at 412 nm and 37°C by adding 20 µL of the stored serum to 200 µL of the Tris buffer containing 2 Mm of $CaCl_2$ and 7 Mm of paraoxon, PON-1 activity was expressed as U/L.

Statistical Analysis

Statistical analyses were performed with the SPSS package program for Windows version 25.0 statistical software (SPSS Inc., Chicago, IL, USA). Gaussian-distributed continuous variables were presented as mean ± standard deviations with their min-max median. Distributions of the numerical variables were analyzed for normality using Kolmogorov-Smirnov test. To analyze the differences, one-tailed t-test for Gaussian variables and Mann–Whitney test for non-Gaussian variables used. Correlations between continuous variables calculated using Pearson test, and Spearmen's rank correlation test was used when appropriate. P value of 0.05 or less was considered statistically significant.

Results

The mean age of the patients are 59,3 ± 13,27 years. Mean HD duration is 6,2±5,5 years. Clinical, demographic and biochemical parameters of patients are shown at table 1. Biochemical parameters of patients between pre HD and post HD are shown at table 2. Post HD PON1 activity measurements were higher than pre HD PON1 measurements, and statistically highly significant (r=0.967, p<0.0001).Post HD serum levels of creatinine, phosphorus, potassium, urea were lower than pre HD levels (r=0,834, r=0,488, r=0,697, r=0,727, p=0,001). Post HD albumin was higher than pre HD albumin (r=0.583, p=0.001). Post HD PON1 activity and post HD pPPT were negatively correlated and statistically highly significant (r=-0.410, p=0.009). Pre HD PON1 levels and pre HD pPTT measurements were negatively correlated and statistically significant (r=-0.381, p=0.014). Post HD PON-1 and postHD E' measurements were positively correlated and statistically significant (r=0.345, p=0.050).

Multiple linear regression analysis was run to predict PON1 levels from pPTT, creatinine, c reactive protein (CRP) and parathormone (PTH), the model statistically significantly predicted relation p<0,05, R=0,527, out of four one variable pPTT (p<0,05) added statistically significant to the prediction and one variable

CRP (p=0,055) is close to statistical significance. Model summary is shown at Table 3 and ANOVA table is shown at Table 4 and coefficient table is shown at Table 5.

pPTT and PON1 activity are found negatively correlated (p<0.009). Post hemodialysis E' is also found positively correlated with PON1 and statistically significant (p=0.050). Post-Hemodialysis PAP and Post-Hemodialysis PON1 are weakly positively correlated and could be statistically significant (p =0.053). Correlation analysis of PON1 activity, echocardiography measurements and pPTT are shown at table 6. Scatter plot graphic for PON1 is shown at Figure 1 and scatter plot graphics for pPTT,E’ and PON1 are shown at Figure 2.

Discussion

Our study showed first time at the literature that there is an independent correlation between pulmonary pulse transit time, an indicator for pulmonary hypertension and pulmonary fibrosis, and PON1. Post hemodialysis PON1 activity and post hemodialysis pulmonary pulse transit time were negatively correlated and statistically highly significant (r=-0.410, p = 0.009). Pre hemodialysis paraoxonase1 levels and pre hemodialysis pulmonary pulse transit time measurements were negatively correlated and statistically significant (r=-0.381, p = 0.014). Multiple linear regression analysis was run to predict paraoxonase1 levels from pulmonary pulse transit time, creatinine, c reactive protein and parathormone, the model statistically significantly predicted relation p < 0,05, R = 0,527, out of four one variable pulmonary pulse transit time (p < 0,05) added statistically significant to the prediction. Post hemodialysis paraoxonase1 and post hemodialysis E’ measurements were also positively correlated and statistically significant (r = 0.345, p = 0.050).

PON1 is an enzyme with potent antioxidant and anti-inflammatory properties (8). PON1 found at HDL has antioxidant and anti-inflammatory effects which PON1 linked with HDL are degradation of hydrogen peroxide and lipid peroxides, prevention of lipoprotein oxidation, reverse cholesterol transport which includes efflux of cholesterol from macrophages and prevention of foam cell formation (1, 4). PON1 activity is decreased at CVD and CKD patients (19). Decrease of PON1 activity is related with atherosclerosis which can be the possible cause of CVD at HD patients (11). Reduction of PON1 activity at ESRD patients is reported to increase CVD risk and may aggravate CVD complications (1, 5, 10).

At our study post hemodialysis PON1 levels were found significantly higher compared to pre dialysis PON1 levels (p < 0.0001). Although PON1 activity is found as decreasing in CKD and HD patients compared to control groups in some number of studies, there is limited research on investigating pre and post dialysis measurements (20). Similar to our study, Gugliucci et al. found that PON1 lactonase activity was significantly higher after dialysis (p < 0.0001) (21). Another study showed an increase at PON1 activity after dialysis ranging from 4–40% (p = 0.001) (22). Higher post hemodialysis PON1 levels of the patients may be attributed to decrease of oxidant parameters during hemodialysis.

Despite the known cardiovascular risk at ESRD patients and possible PON1 effects on it, as Duni et al. stated there is a paucity of data regarding the role of PON1 in alterations of cardiac structure induced by

CKD (1). At this study we investigated various echocardiography measurements with PON1 at hemodialysis patients. In our study, a negative correlation was found between pPTT and PON1 activity ($p = 0.009$), furthermore we found an independent association between PON1 and pPTT. Post hemodialysis E' is also found positively correlated with PON1 and statistically significant ($p = 0.050$). Chronic inflammatory state at ESRD patients, accumulation of uremic toxins, HDL subclass alterations, impairment of HDL function, production of AGEs which overwhelms anti-oxidant capacity and genetic polymorphisms of PON1 may have a role at PON1's mechanism at these findings.

Oxidative stress and inflammation have a major role at pathophysiologic mechanism of vascular injury, atherosclerosis and cardiac remodeling which leads to CVD. PON1 is an enzyme with antioxidative and anti-inflammatory properties whose reduced activity contributes to development of CVD. At animal models, PON1 knockout rats showed faster atherosclerosis development (23) and loss of PON1 in salt-sensitive hypertensive rats resulted in compromised left ventricular function and hypertrophy, increased cardiac fibrosis and macrophage infiltration (24). Assessment of mitral annular velocity plays an essential role in the evaluation of left ventricular diastolic dysfunction. Previous studies showed lower E' velocities at stage 4 and 5 CKD patients ($p < 0.05$) (25). At our study post hemodialysis E' found positively correlated with PON1 and statistically significant ($p = 0.050$).

At a study PON1 levels are found correlated with aortic stiffness index, aortic strain, and aortic distensibility at CKD patients and control group ($p < 0.001$, $p < 0.001$, and $p < 0.001$) (26). pPTT is an important and novel measurement for assessing increased arterial stiffness and pulmonary hemodynamic alterations which refers to the time it takes the pulse pressure wave to travel from one arterial site to another. It is a noninvasive method which is a valuable parameter for determining PH and PF. Oxidative stress has a major role at development and progression of CKD and pulmonary hypertension at CKD patients and oxidative stress is more prominent at HD. Time interval for the pressure pulse wave to travel from the pulmonary valve to the left atrium is defined as pulmonary pulse transit time. pPPT is estimated as the delay between the ventricular electrical activity in the ECG and the arrival of the pulse wave in the pulmonary vein as determined by Doppler echocardiography of the pulmonary vein flow. pPPT measurements are reported decreased at PH patients compared to control group (138.0 ± 16.78 msec; $P < 0.0001$). Patients with both PH and PF have significantly shorter pPTT than patients with PH alone (93.50 ± 15.47 msec; $P = 0.004$) (18). Our study showed first time at the literature that there is an independent correlation between pPTT, an indicator for PH and PF, and PON1. Multiple linear regression analysis was run to predict PON1 levels from pPTT, Creatinine, CRP and PTH, the model statistically significantly predicted relation $p < 0,05$, $R = 0,527$, out of four one variable PPTT($p < 0,05$) added statistically significant to the prediction and one variable CRP ($p = 0,055$) is close to statistical significance. PON1 may have an important role at the pathogenesis of pulmonary hypertension. To our knowledge, this is the first study investigating relation between PON1 activity and pPTT, e' measurements at pre HD and post HD patients.

Conclusion

Our study showed first time at the literature that there is an independent correlation between pPTT, an indicator for PH and PF, and PON1 may have an important role at the pathogenesis of pulmonary hypertension. Further studies are needed on this subject. Our study has a few limitations that it has a small sample size and doesn't have a control group.

Declarations

Conflict Of Interest Statement

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

References

1. Duni A, Liakopoulos V, Rapsomanikis KP, Dounousi E. Chronic Kidney Disease and Disproportionally Increased Cardiovascular Damage: Does Oxidative Stress Explain the Burden?. *Oxid Med Cell Longev*. 2017;2017:9036450. doi:10.1155/2017/9036450
2. GUGLIUCCI, Alejandro; KOTANI, Kazuhiko; KIMURA, Satoshi. Paraoxonase 1 in chronic kidney failure. *Journal of Lipids*, 2012, 2012.
3. Marques, F.S., Da Silva, A.L.M., Mattoso, R.J.C., Aras, R., De Oliveira, R.J.B., De Abreu Santos, J.C., Couto, F.D. and Couto, R.D. (2017) Low-Flow Polysulfone Hemodialysis Alters Lipoprotein Parameters, Paraoxonase Activity and in Vitro Incorporation of Phospholipids. Journal of Biophysical Chemistry, 8, 23-38. https://doi.org/10.4236/jbpc.2017.83003
4. Duni A, Liakopoulos V, Roumeliotis S, Peschos D, Dounousi E. Oxidative Stress in the Pathogenesis and Evolution of Chronic Kidney Disease: Untangling Ariadne's Thread. *Int J Mol Sci*. 2019;20(15):3711. Published 2019 Jul 29. doi:10.3390/ijms20153711
5. Liakopoulos V, Roumeliotis S, Zarogiannis S, Eleftheriadis T, Mertens PR. Oxidative stress in hemodialysis: Causative mechanisms, clinical implications, and possible therapeutic interventions. *Semin Dial*. 2019;32(1):58-71. doi:10.1111/sdi.12745
6. Fortuño A, Beloqui O, San José G, Moreno MU, Zalba G, Díez J. Increased phagocytic nicotinamide adenine dinucleotide phosphate oxidase-dependent superoxide production in patients with early chronic kidney disease. *Kidney Int Suppl*. 2005;(99):S71-S75. doi:10.1111/j.1523-1755.2005.09913.x
7. Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. *Oxid Med Cell Longev*. 2017;2017:3081856. doi:10.1155/2017/3081856
8. Furlong CE, Marsillach J, Jarvik GP, Costa LG. Paraoxonases-1, -2 and -3: What are their functions?. *Chem Biol Interact*. 2016;259(Pt B):51-62. doi:10.1016/j.cbi.2016.05.036

9. Mohammed CJ, Xie Y, Brewster PS, et al. Circulating Lactonase Activity but Not Protein Level of PON-1 Predicts Adverse Outcomes in Subjects with Chronic Kidney Disease. *J Clin Med*. 2019;8(7):1034. Published 2019 Jul 15. doi:10.3390/jcm8071034
10. Suematsu Y, Goto M, Park C, et al. Association of Serum Paraoxonase/Arylesterase Activity With All-Cause Mortality in Maintenance Hemodialysis Patients. *J Clin Endocrinol Metab*. 2019;104(10):4848-4856. doi:10.1210/jc.2019-00334
11. Chang CT, Lim YP, Lee CW, et al. PON-1 carbamylation is enhanced in HDL of uremia patients. *J Food Drug Anal*. 2019;27(2):542-550. doi:10.1016/j.jfda.2018.09.007
12. Yigla M, Nakhoul F, Sabag A, et al. Pulmonary hypertension in patients with end-stage renal disease. *Chest*. 2003;123(5):1577-1582. doi:10.1378/chest.123.5.1577
13. Kawar B, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. *Am J Nephrol*. 2013;37(3):281-290. doi:10.1159/000348804
14. Pabst S, Hammerstingl C, Hundt F, Gerhardt T, Grohe´ C, et al. (2012) Pulmonary Hypertension in Patients with Chronic Kidney Disease on Dialysis and without Dialysis: Results of the PEPPER-Study. PLoS ONE 7(4): e35310. doi:10.1371/journal.pone.0035310
15. Reque J, Garcia-Prieto A, Linares T, et al. Pulmonary Hypertension Is Associated with Mortality and Cardiovascular Events in Chronic Kidney Disease Patients. *Am J Nephrol*. 2017;45(2):107-114. doi:10.1159/000453047
16. Yigla M, Keidar Z, Safadi I, Tov N, Reisner SA, Nakhoul F. Pulmonary calcification in hemodialysis patients: correlation with pulmonary artery pressure values. *Kidney Int*. 2004;66(2):806-810. doi:10.1111/j.1523-1755.2004.00807.x
17. Ambroz, D., et al. "Predictors of survival in patients with pulmonary hypertension and acute right heart failure." *Bratislavske lekarske listy* 121.3 (2020): 230-235.
18. Wibmer T, Rüdiger S, Scharnbeck D, et al. Pulmonary pulse transit time: a novel echocardiographic indicator of hemodynamic and vascular alterations in pulmonary hypertension and pulmonary fibrosis. *Echocardiography*. 2015;32(6):904-911. doi:10.1111/echo.12772
19. Kunutsor SK, Bakker SJ, James RW, Dullaart RP. Serum paraoxonase-1 activity and risk of incident cardiovascular disease: The PREVEND study and meta-analysis of prospective population studies. *Atherosclerosis*. 2016;245:143-154. doi:10.1016/j.atherosclerosis.2015.12.021
20. Sztanek, Ferenc, et al. "Decreased paraoxonase 1 (PON1) lactonase activity in hemodialyzed and renal transplanted patients. A novel cardiovascular biomarker in end-stage renal disease." *Nephrology Dialysis Transplantation* 27.7 (2012): 2866-2872
21. Gugliucci A, Kinugasa E, Kotani K, Caccavello R, Kimura S. Serum paraoxonase 1 (PON1) lactonase activity is lower in end-stage renal disease patients than in healthy control subjects and increases after hemodialysis. *Clin Chem Lab Med*. 2011;49(1):61-67. doi:10.1515/CCLM.2011.004
22. Gugliucci A, Mehlhaff K, Kinugasa E, et al. Paraoxonase-1 concentrations in end-stage renal disease patients increase after hemodialysis: correlation with low molecular AGE adduct clearance. *Clin Chim Acta*. 2007;377(1-2):213-220. doi:10.1016/j.cca.2006.09.028

23. Gungor O, Kircelli F, Demirci MS, et al. Serum paraoxonase 1 activity predicts arterial stiffness in renal transplant recipients. *J AtherosclerThromb*. 2011;18(10):901-905. doi:10.5551/jat.9175
24. Shih DM, Xia YR, Wang XP, et al. Combined serum paraoxonase knockout/apolipoprotein E knockout mice exhibit increased lipoprotein oxidation and atherosclerosis. *J Biol Chem*. 2000;275(23):17527-17535. doi:10.1074/jbc.M910376199
25. Hayashi, Shirley Yumi, et al. "Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging." *Nephrology Dialysis Transplantation* 21.1 (2006): 125-132
26. Efe TH, Ertem AG, Altunoglu A, et al. Serum Paraoxonase Levels are Correlated with Impaired Aortic Functions in Patients with Chronic Kidney Disease. *Acta Cardiol Sin*. 2016;32(1):75-80. doi:10.6515/acs20150429a

Tables

Mean (±SD)		Mean (±SD)	
Mean age (Years ± SD)	59.3±13.27	PDW	2.1±2.2
Male % (n)	0.39 (14/36)	ALT (U/L)	10.1±6.0
Diabetes Mellitus	8/36	AST (U/L)	12.4±5.7
Chronic Heart Failure	5/36	CK (U/L)	64.2±38.0
Angiography	12/36	GGT (U/L)	46.6±99.5
CABG	7/36	ALP (U/L)	148.3±82.6
Smoking Habit	10/36	Triglyceride (mg/dl)	177.3±108.0
CKD (years)	7.0 ±5.32	Total Cholesterol (mg/dl)	151.7±39.8
WBC	7730.1 ±2579	LDL (mg/dl)	82.5±29.0
HGB	11.1±1.2	Direct Bilirubin (mg/dl)	0.45±1.8
MCH	29.1±1.75	Na (mmol/L)	137.0±2.8
MCHC	32.2±0.9	Cl (mmol/L)	98.3±3.2
RDW	14.4±1.2	Fe (mg/dl)	46.8±18.8
PLT	203.2±53.7	TIBC (mg/dl)	221.9±70.3
NEU	5.1±2.2	ASO (U/ml)	108.4±106.6
LYM	1.7±0.5	CRP (mg/L)	3.15±10.5
MONO	0.6±0.2	B12 (pg/ml)	359.2±231.1
BASO	0.04±0.02	Ferritin (mg/L)	449.1±219.0
MPV	10.5±0.9	Folate (ng/ml)	7.3±4.6
PCT	0.2±0.05	PTH (ng/L)	357.9±311.5

Table 1. Clinical, demographic and biochemical parameters of patients

	Pre Hemodialysis (n=36)	Post Hemodialysis (n=36)	Correlations**	p-values*
Albumin(g/l)	4.07±0.35	4.6±0.57	0.583	0.001
P	4.68±1.32	2.21±0.63	0.488	0.001
Ca	8.7±0.71	10.1±0.75	-0.129	0.454
K	5.7±0.69	3.78±0.53	0.697	0.001
Total Protein	7.06±0.54	7.75±0.77	0.168	0.328
GFR	4.9±1.52	17.1±4.92	0.673	0.001
Creatinine(µmol/l)	9.33±2.6	3.38±1.0	0.834	0.001
Urea	160.9±34	49.1±14.3	0.727	0.001
Glucose	115.3 ±61.6	103.9±28.3	0.337	0.253
Na	136.9±2.8	138.3±1.9	-0.129	0.04
Paraoxonase-1(u/l)	164.5±27.4	270.2±153.5	0.967	<0.001

*Post-hemodialysis values compared to pre-hemodialysis values.

**Correlations between pre-hemodialysis and post-hemodialysis values.

Table 2. Biochemical parameters of patients between pre HD and post HD

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.527[a]	.278	.175	140.36571	.278	2.696	4	28	.047

a. Predictors: (Constant), pPTT, PTH, CRP, Creatinine

b. Dependent Variable: PON1

Table 3. Model summary

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	212460.570	4	53115.143	2.696	.047[b]
	Residual	551670.945	28	19702.534		
	Total	764131.515	32			

a. Dependent Variable: Paraoxonase

b. Predictors: (Constant), pPTT, Parathormone, CRP, Creatinine

Table 4. ANOVA result of model.

Coefficients[a]

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
tant)	1519.850	519.706		2.924	.007	455.281	2584.420
	-7.699	3.023	-.412	-2.547	.017	-13.892	-1.507
	4.956	2.470	.350	2.006	.055	-.105	10.016
nine	8.204	9.739	.139	.842	.407	-11.745	28.153
	-.121	.088	-.246	-1.373	.181	-.302	.060

ıdent Variable: Paraoxonase

Table 5. Coefficients of the model.

Variable	PON1 Activity (µg / mL)		
	Correlation	p-value	Mean±SD
Pre-Hemodialysis pPTT	-0.381	0.014*	166.37±10.7 msec
Post-Hemodialysis pPTT	-0.410	0.009*	194.88±10.9 msec
Pre-Hemodialysis E’	0.113	0.266	62±8.01 cm/s
Post-Hemodialysis E’	0.345	0.050*	77.07±12.8 cm/s
Post-Hemodialysis PON1	0.967	<0.0001*	270.2±153.5 u/L
Pre-Hemodialysis TAPSE	-0.090	0.310	2.47±0.104 cm
Post-Hemodialysis TAPSE	-0.174	0.167	2.65±0.108 cm
Pre-Hemodialysis PAP	0.170	0.172	30.58±5.16 mmHg
Post-Hemodialysis PAP	0.286	0.053	27.49±4.60 mmHg
Pre-Hemodialysis MPI	-0.004	0.492	0.540±0.056
Post-Hemodialysis MPI	0.069	0.351	0.477±0.051
Pre-Hemodialysis E/A	0.049	0.394	1.01±0.277
Post-Hemodialysis E/A	0.101	0.289	1.03±0.283
EF	0.280	0.98	52.576±2.64 %
LA	-0.136	0.451	4.437±5.103 cm
IVS	-0.202	0.260	1.137±0.13 cm
PWT	-.0163	0.365	1.127±0.107 cm

Table6.Correlation analysis of PON1 activity, echocardiography measurements and pPTT

Figures

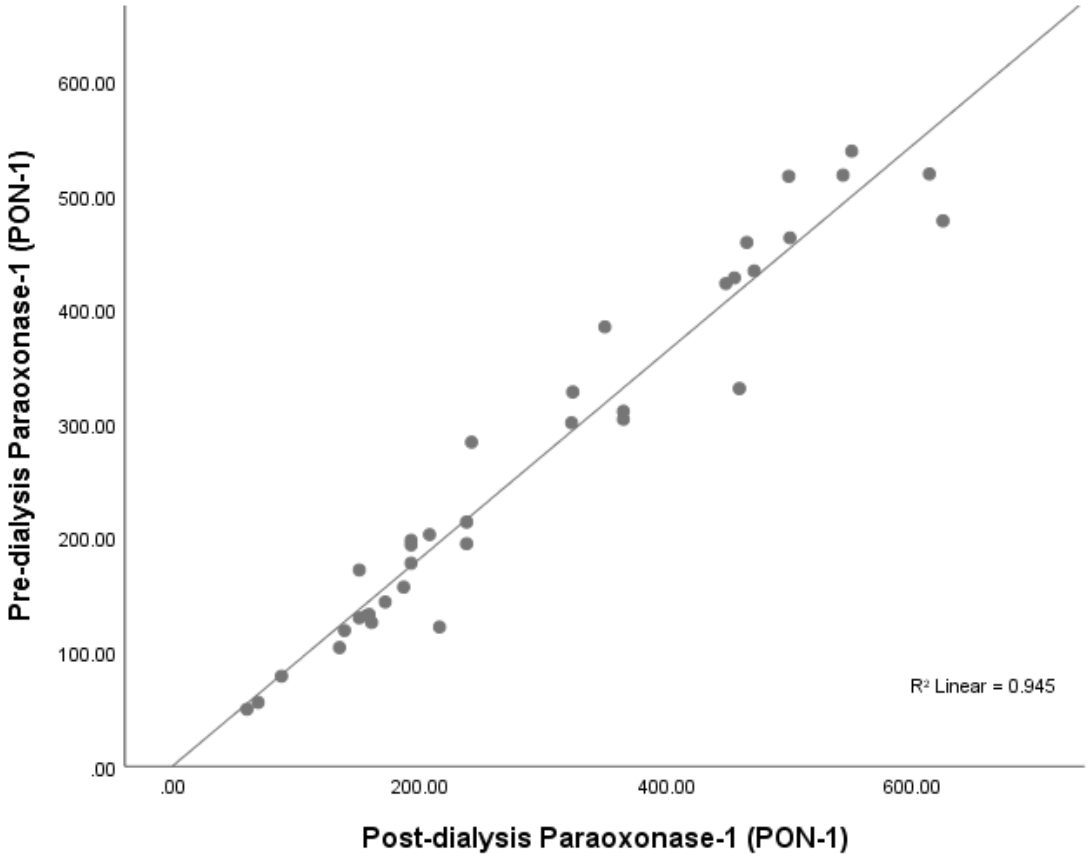

Figure 1

Scatter plot graphic for PON1 before and after hemodialysis

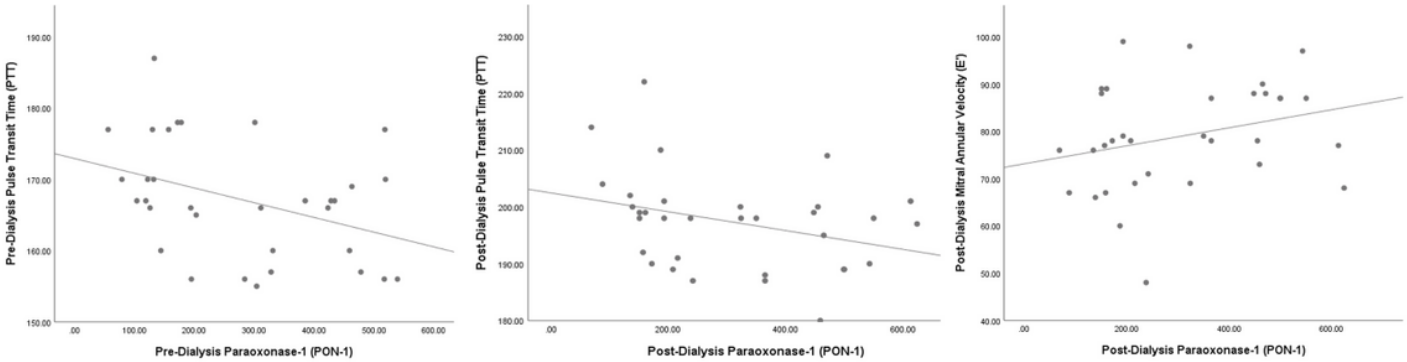

Figure 2

Scatter plot graphics for pPTT,E’ and PON1