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Independent Association Between Paraoxonase 1 and Pulmonary Pulse Transit Time in Patients Undergoing Hemodialysis

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Abstract: Pulmonary hypertension (PH) and pulmonary fibrosis are significant complications of hemodialysis. Pulmonary pulse transit time (pPTT) is a valuable non-invasive marker for assessing these conditions. Paraoxonase 1 (PON1) has strong antioxidant and anti-inflammatory properties, making it effective in combatting oxidative stress and inflammation. Its effectiveness in these areas suggests that it may be associated with echocardiographic parameters in hemodialysis patients. This study examines the correlation between PON1 and echocardiographic parameters in this specific patient group. The study included a total of 36 patients receiving maintenance hemodialysis for at least three months were included in this study. Blood samples and echocardiographic assessments were obtained before and after the hemodialysis sessions. The mean age of the participants was 59.3 ± 13.27 years, with an average hemodialysis duration of 6.2 ± 5.5 years. Post-hemodialysis PON1 activity was significantly higher than pre-hemodialysis levels ($r = 0.967$, $p < 0.0001$). Negative correlations were observed between post-hemodialysis PON1 and post-hemodialysis pPTT ($r = -0.410$, $p = 0.009$), between pre-hemodialysis PON1 and pre-hemodialysis pPTT ($r = -0.381$, $p = 0.014$). Additionally, post-hemodialysis PON1 was positively correlated with post-hemodialysis early diastolic mitral annular velocity (E') ($r = 0.345$, $p = 0.050$). Multiple linear regression analysis revealed that pPTT ($p < 0.05$) was a statistically significant predictor of PON1 activity, while C-Reactive Protein (CRP) ($p = 0.055$) approached statistical significance ($R = 0.527$, $p < 0.05$). This study is the first to report an independent association between Pptt, an indicator of pulmonary hypertension (PH) and pulmonary fibrosis—and PON1 activity in hemodialysis patients. These findings suggest that PON1 may play a role in the pathophysiology of pulmonary complications in this population.

Keywords: hemodialysis, pulmonary hypertension, pulmonary fibrosis, paraoxonase 1, chronic kidney disease

Hemodiyaliz Hastalarında Paraoksonaz 1 ile Pulmoner Nabız Geçiş Süresi Arasındaki Bağımsız İlişki

Özet: Pulmoner hipertansiyon (PH) ve pulmoner fibrozis hemodiyalizde önemli komplikasyonlardır. Pulmoner nabız geçiş süresi (pPTT), bu durumları değerlendirmek için değerli bir non-invaziv belirteç görevi görür. Paraoksonaz 1 (PON1), güçlü antioksidan ve anti-inflamatuar özellikler sergiler ve bu da onu oksidatif stres ve inflamasyonla mücadelede güçlü bir ajan yapar. Bu alanlardaki etkinliği, potansiyel faydalarını vurgular ve hemodiyaliz hastalarında ekokardiyografik parametrelerle ilişkilendirilebilir. Bu çalışma, bu özel hasta grubunda PON1 ile ekokardiyografik parametreler arasındaki korelasyonu incelemeyi amaçlamaktadır. Bu çalışmaya en az üç ay boyunca rutin hemodiyaliz alan toplam 36 hasta dahil edildi. Kan örnekleri ve ekokardiyografik değerlendirmeler hemodiyaliz seanslarından önce ve sonra alındı. Katılımcıların ortalama yaşı 59,3 ± 13,27 yıldı ve ortalama hemodiyaliz süresi 6,2 ± 5,5 yıldı. Hemodiyaliz sonrası PON1 aktivitesi hemodiyaliz öncesi seviyelere

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kıyasla önemli ölçüde yüksekti (r = 0,967, p < 0,0001). Hemodiyaliz sonrası PON1 ile hemodiyaliz sonrası pPTT (r = -0,410, p = 0,009) ve hemodiyaliz öncesi PON1 ile hemodiyaliz öncesi pPTT (r = -0,381, p = 0,014) arasında negatif bir korelasyon gözlendi. Ek olarak, hemodiyaliz sonrası PON1, hemodiyaliz sonrası erken diyastolik mitral anüler hız (E') ile pozitif korelasyon gösterdi (r = 0,345, p = 0,050). Çoklu doğrusal regresyon analizi, pPTT'nin (p < 0,05) PON1'in istatistiksel olarak anlamlı bir öngörücüsü olduğunu, CRP'nin (p = 0,055) ise istatistiksel anlamlılığa yakın olduğunu (R = 0,527, p < 0,05) ortaya koydu. Bu çalışma, hemodiyaliz hastalarında PH ve pulmoner fibrozisin bir göstergesi olan pPTT ile PON1 aktivitesi arasında bağımsız bir ilişki olduğunu bildiren ilk çalışmadır. Bu bulgular, PON1'in bu popülasyonda pulmoner komplikasyonların patofizyolojisinde rol oynayabileceğini düşündürmektedir.

Anahtar kelimeler: hemodiyaliz, pulmoner hipertansiyon, pulmoner fibrozis, paraoksonaz 1, kronik böbrek hastalığı

INTRODUCTION

Patients with end-stage renal disease (ESRD) face a markedly elevated risk of developing cardiovascular disease (CVD)—estimated to be nearly tenfold higher than in the general population (Duni et al,2017). Mounting evidence suggests that oxidative stress (OS) and chronic inflammation are central contributors to the pathophysiology of CVD in hemodialysis (HD) patients (Duni et al,2017; Duni et al, 2019; Gugliucci et al, 2012; Marques et al, 2017).

Chronic kidney disease (CKD) is characterized by an imbalance between oxidative stress and antioxidant defense mechanisms, leading to persistent inflammation, endothelial dysfunction, and systemic complications such as cardiovascular disease (Marques et al, 2017). The burden of oxidative stress is particularly pronounced in ESRD patients undergoing maintenance hemodialysis, where increased production of reactive oxygen species (ROS) and nitrogen species, including nitric oxide (NO), results in accelerated tissue damage (Liakopoulos et al, 2019). This oxidative burden is primarily driven by enzymatic activation (e.g., NADPH oxidase, xanthine oxidase, and lipoxygenase), mitochondrial dysfunction, and depletion of key antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Daenen et al, 2018; Duni et al,2017; Liakopoulos et al, 2019; Liakopoulos et al, 2017). Moreover, the dialysis process itself exacerbates oxidative stress, depleting antioxidants and increasing the accumulation of oxidative by-product (Duni et al,2017; Liakopoulos et al, 2019; Liakopoulos et al, 2017).

The interplay between oxidative stress and inflammation in ESRD contributes to vascular dysfunction, endothelial damage, and the progression of atherosclerosis, all of which significantly heighten CVD risk (Duni et al,2017). Cardiac remodeling is triggered by ROS-mediated signaling pathways, leading to several key changes, including myocardial apoptosis, fibrosis, diastolic dysfunction, and chamber dilation. This sequence highlights the interconnected effects of these processes on heart health. These processes are mediated by the activation of promitogenic kinases, transcription factors, and matrix metalloproteinases, leading to progressive cardiac deterioration (Duni et al,2017).

Among the key antioxidant defense systems, paraoxonase (PON) enzymes, particularly PON1, PON2, and PON3, play an essential role in neutralizing oxidative damage and regulating inflammatory responses (Furlong et al, 2016). Paraoxonase 1 (PON1) is an enzyme with strong antioxidant and anti-inflammatory properties, making it a valuable agent against oxidative stress and inflammation. PON1, a glycoprotein with esterase and lactonase activity, is primarily synthesized in the liver and transported in circulation via high-density lipoproteins (HDLs) (Furlong et al, 2016; Mohammed et al, 2019). It contributes to lipoprotein stability, hydrolyzes lipid peroxides, and prevents low-density lipoprotein (LDL) oxidation, thereby reducing atherosclerosis risk (Duni et al,2017; Liakopoulos et al, 2019;

Suematsu et al, 2019). A decline in PON1 activity has been implicated in the pathogenesis of atherosclerosis and cardiovascular complications in hemodialysis patients (Chang et al, 2019).

Pulmonary hypertension (PH) and pulmonary fibrosis (PF) are increasingly recognized as serious complications in hemodialysis patients (Kawar et al, 2013; Walther et al, 2020, Pabst et al, 2012). The prevalence of these conditions is notably high in this population, and their development is closely tied to oxidative stress and systemic inflammation (Kawar et al, 2013; Walther et al, 2020; Pabst et al, 2012). PH and PF significantly worsen clinical outcomes, as they are independently associated with increased cardiovascular morbidity and mortality (Reque et al, 2016). Diagnosing PH and PF at an early stage is challenging because symptoms often remain asymptomatic until advanced stages. Furthermore, fluid overload-related dyspnea in hemodialysis patients complicates the differentiation of PH from other causes (Pabst et al, 2012).

The pathophysiology of PH and PF in hemodialysis patients is multifactorial and includes ROS-induced endothelial dysfunction, nitric oxide depletion, increased fibrin deposition, endothelin-mediated vasoconstriction, and vascular calcification (Kawar et al, 2013; Walther et al, 2020; Tang et al, 2018). Chronic hemodynamic stress, coupled with activation of pro-fibrotic growth factors such as TGF-β, PDGF, and FGF, leads to smooth muscle cell proliferation and fibrosis (Kawar et al, 2013; Walther et al, 2020; Tang et al, 2018). Although right heart catheterization remains the gold standard for PH diagnosis, its invasive nature limits its use in routine clinical practice (Ambroz et al, 2020). In contrast, pulmonary pulse transit time (pPTT) has emerged as a non-invasive and reliable echocardiographic marker for assessing pulmonary vascular alterations, PH, and PF (Wibmer et al, 2014).

Given the established link between oxidative stress, cardiovascular pathology, and pulmonary complications in hemodialysis patients, PON1 may play a pivotal role in modulating these processes. However, research exploring the relationship between PON1 activity and echocardiographic parameters, particularly pPTT, in hemodialysis patients is limited.

This study aims to investigate the association between PON1 activity and echocardiographic parameters, including early diastolic mitral annular velocity (E′), pulmonary artery pressure (PAP), tricuspid annular peak systolic excursion (TAPSE), myocardial performance index (MPI), E/A ratio, posterior wall thickness (PWT), interventricular septum thickness (IVS), left atrium diameter (LA), ejection fraction (EF), and pPTT before and after hemodialysis. Our goal is to determine whether PON1 is independently associated with pPTT and other echocardiographic markers of pulmonary fibrosis and hypertension.

MATERIALS and METHODS

This study included 36 patients diagnosed with end-stage renal disease (ESRD) who had been receiving maintenance hemodialysis for a minimum duration of three months. All participants underwent three hemodialysis sessions per week, each lasting four hours. Inclusion criteria required that patients be clinically stable and free from acute infections or recent hospitalizations. Patients with malignancies, sepsis, hepatic dysfunction, connective tissue disorders, or other inflammatory conditions were excluded from the study to minimize potential confounding factors that could influence oxidative stress parameters.

The study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the Ahi Evran University Faculty of Medicine Research Ethics Committee (Approval No: 2020-19/135, Date: 22/12/2020). Before participation, all patients provided written informed consent.

All participants underwent a comprehensive medical history review and clinical examination. Data on demographic characteristics, including age, sex, smoking status, and hemodialysis duration, were collected. Blood samples were obtained both before and after hemodialysis. Pre-hemodialysis blood samples were collected after an overnight fast, whereas post-hemodialysis samples were taken immediately after the session, prior to heparin administration, through the arterial line of the dialysis circuit.

Venous blood was drawn from the antecubital vein and processed for biochemical analysis. Samples were divided into standard biochemistry tubes and tubes containing K_2EDTA. After clot formation, biochemistry tubes were centrifuged at 3,000 rpm for 10 minutes, and serum was separated into aliquots and stored at −80°C until paraoxonase 1 (PON1) activity was analyzed. Complete blood count (CBC) measurements were performed using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Japan), while routine biochemical parameters were assessed with an automated biochemistry analyzer (Cobas 8000, Roche Diagnostics, Mannheim, Germany). PON1 activity was determined spectrophotometrically using a commercial assay kit (Relassay, Gaziantep, Turkey) on a Cobas C 501 autoanalyzer (Roche Diagnostics, Mannheim, Germany). The assay was based on the hydrolysis rate of diethyl-p-nitrophenyl phosphate in the presence of sodium chloride, measured at an absorbance of 412 nm and a temperature of 37°C. PON1 activity was expressed in units per liter (U/L).

Echocardiographic evaluations were performed before and after hemodialysis by an experienced cardiologist who was blinded to patient data and study hypotheses. A standard transthoracic echocardiography system was used following the guidelines of the American Society of Echocardiography (ASE). Pulmonary pulse transit time (pPTT) was assessed using pulse-wave Doppler imaging from the right superior pulmonary vein, measuring the time interval between the R wave on the electrocardiogram (ECG) and the corresponding peak late systolic pulmonary vein flow velocity. Early diastolic mitral annular velocity (E′) was determined using tissue Doppler imaging, while pulmonary artery pressure (PAP) was estimated via tricuspid regurgitant jet velocity. Other echocardiographic parameters included tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI), E/A ratio, left atrial diameter (LA), left ventricular ejection fraction (EF), posterior wall thickness (PWT), and interventricular septum thickness (IVS). Doppler measurements were performed with simultaneous ECG recordings, and values were averaged over three consecutive cardiac cycles to improve measurement accuracy.

All statistical analyses were conducted using SPSS Statistics for Windows, version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables were presented as means with standard deviations, while non-normally distributed data were reported as medians with interquartile ranges. Pre- and post-hemodialysis values were compared using paired t-tests for normally distributed variables, whereas non-parametric comparisons were performed using the Wilcoxon signed-rank test. Correlations between variables were analyzed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-parametric variables. A multiple linear regression model was employed to identify independent predictors of PON1 activity, incorporating pPTT, creatinine, C-reactive protein (CRP), and parathyroid hormone (PTH) as independent variables. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 36 patients with end-stage renal disease undergoing maintenance hemodialysis. The mean age of the participants was 59.3 ± 13.27 years, and the average duration of hemodialysis treatment was 6.2 ± 5.5 years. Among the patients, 60% were female (22/36), 22% had diabetes mellitus (8/36), and 14% had a history of chronic heart failure (5/36). Additionally, 33% of the patients had undergone coronary angiography (12/36), and 19% had a history of coronary artery bypass grafting (CABG) (7/36). The clinical and demographic characteristics of the patients are summarized below, presented in Table 1.

Table 1. Clinical, demographic and biochemical parameters of patients.

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

*CABG (coronary artery bypass graft), TAPSE (tricuspid annular plane systolic excursion), PWT (posterior wall thickness).

Biochemical parameters were assessed before and after the hemodialysis session, with the results summarized in Table 2. Post-hemodialysis PON1 activity was significantly higher than pre-hemodialysis levels ($r = 0.967$, $p < 0.0001$). Additionally, post-hemodialysis serum concentrations of creatinine, phosphorus, potassium, and urea were markedly lower than pre-hemodialysis values ($r = 0.834$, $r = 0.488$, $r = 0.697$, $r = 0.727$, respectively; $p = 0.001$ for all comparisons). In contrast, post-hemodialysis albumin levels were significantly elevated compared to pre-hemodialysis values ($r = 0.583$, $p = 0.001$).

A significant negative correlation was observed between post-hemodialysis PON1 and post-hemodialysis pPTT ($r = -0.410$, $p = 0.009$), as well as between pre-hemodialysis PON1 and pre-hemodialysis pPTT ($r = -0.381$, $p = 0.014$). Furthermore, post-hemodialysis PON1 levels were positively

correlated with post-hemodialysis early diastolic mitral annular velocity (E′), with the relationship reaching statistical significance (r = 0.345, p = 0.050).

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

	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/)	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.

Multiple linear regression analysis was conducted to evaluate whether pPTT, creatinine, CRP, or PTH independently predicted PON1 activity. The regression model significantly predicted PON1 levels (R = 0.527, p < 0.05). Among the included variables, pPTT demonstrated a statistically significant contribution to PON1 prediction (p < 0.05), while CRP exhibited a trend toward significance (p = 0.055). The regression model summary, ANOVA results, and regression coefficients are provided in Tables 3, 4, and 5, respectively.

Table 3. Model summary.

Model Summary[b]									
				Std. Error	Change Statistics				
Model	R	R^2	Adjusted R^2	of the Estimate	R^2 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 4. ANOVA result of model.

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 5. Coefficients of the model.

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

a. Dependent Variable: Paraoxonase

Correlation analyses of PON1 activity with pPTT and echocardiographic parameters revealed a significant inverse association between pPTT and PON1 activity (p = 0.009). Additionally, a positive correlation was identified between post-hemodialysis PON1 and post-hemodialysis E′, reaching statistical significance (p = 0.050). Post-hemodialysis PON1 and post-hemodialysis PAP exhibited a weak positive correlation, which approached statistical significance (p = 0.053). A detailed summary of correlation coefficients is provided in Table 6.

Table 6. Correlation analysis of PON1 activity, echocardiography measurements and pPTT.

	PON1 Activity (μg / mL)		
Variable	**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

Scatter plots illustrating the relationships between PON1 levels before and after hemodialysis, as well as the associations among pPTT, E′, and PON1, are presented in Figures 1 and 2.

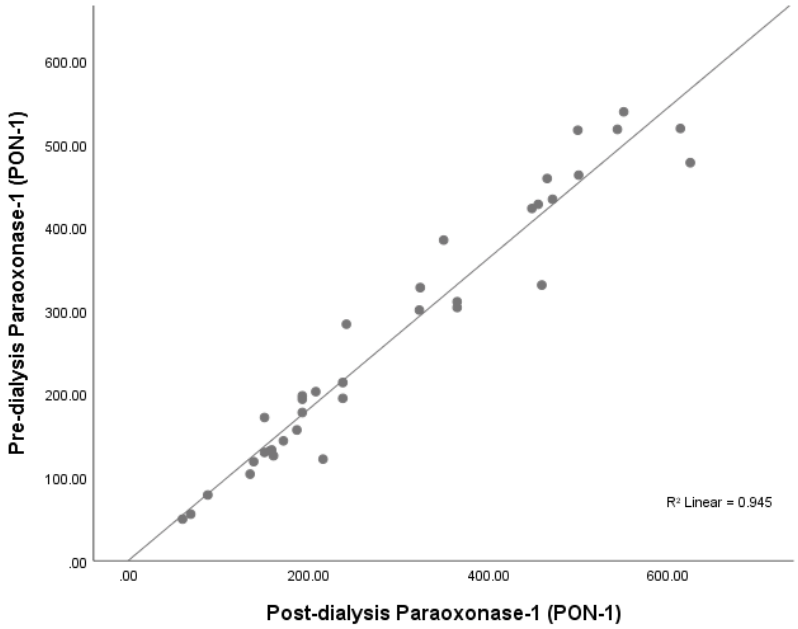

Figure. 1. Scatter plot graphic for PON1 before and after hemodialysis.

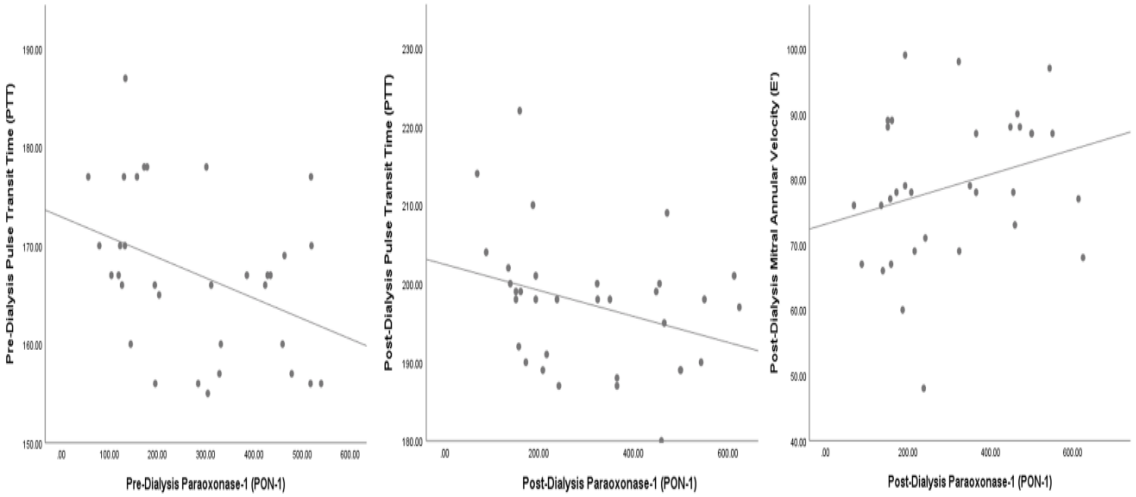

Figure. 2. Scatter plot graphics for pPTT,E' and PON1.

DISCUSSION and CONCLUSION

This study offers new evidence on the association between paraoxonase 1 (PON1) activity and pulmonary pulse transit time (pPTT) in individuals receiving hemodialysis. To our knowledge, this is the first report to identify an independent relationship between PON1 levels and pPTT—an established echocardiographic indicator of pulmonary hypertension and pulmonary fibrosis. We observed that PON1 activity significantly increased following hemodialysis and showed a consistent inverse correlation with pPTT both pre- and post-dialysis. Additionally, post-dialysis PON1 levels were positively associated with early diastolic mitral annular velocity (E′), indicating a possible connection between PON1 and left ventricular diastolic function.

PON1 is a potent antioxidant and anti-inflammatory enzyme that plays a crucial role in protecting against oxidative stress and lipid peroxidation (Furlong et al, 2016). The enzyme is primarily associated with high-density lipoproteins (HDL), where it contributes to lipoprotein stability, neutralization of lipid peroxides, and inhibition of low-density lipoprotein (LDL) oxidation (Duni et al, 2017; Liakopoulos et al, 2019; Suematsu et al, 2019). Reduced PON1 activity has been implicated in the pathogenesis of atherosclerosis and cardiovascular disease (CVD), particularly in patients with chronic kidney disease (CKD) and those undergoing hemodialysis (Chang et al, 2019). Consistent with this, prior studies have reported that PON1 activity is lower in patients with CKD and inversely related to cardiovascular risk (Kunutsor et al, 2016). The observed increase in post-hemodialysis PON1 activity in our study aligns with previous research suggesting that hemodialysis may transiently improve PON1 function (Sztanek et al, 2012). This increase could be attributed to the removal of oxidant molecules during dialysis, which may alleviate oxidative burden and enhance antioxidant enzyme activity. Gugliucci et al. similarly reported a significant rise in PON1 lactonase activity following hemodialysis, further supporting this hypothesis (Gugliucci et al, 2007).

Despite the well-established cardiovascular risks associated with CKD and the potential protective role of PON1, few studies have investigated its impact on echocardiographic parameters in hemodialysis patients (Duni et al, 2017). Our study identified a negative correlation between PON1 activity and pPTT, indicating that higher PON1 activity is associated with lower pPTT values. Given that shortened pPTT is a recognized indicator of PH and PF, these findings suggest that PON1 may play a protective role in pulmonary hemodynamics. The pathophysiology of PH and PF in CKD patients is complex, involving endothelial dysfunction, oxidative stress, chronic inflammation, and dysregulated nitric oxide metabolism (Walther et al, 2020; Kawar et al, 2013; Pabst et al, 2012). The observed relationship between PON1 and pPTT in our study provides further evidence that oxidative stress and its modulation by antioxidant enzymes may influence pulmonary vascular changes in hemodialysis patients.

Previous studies have demonstrated that pPTT is significantly reduced in patients with PH and PF, highlighting its utility as a non-invasive diagnostic tool (Wibmer et al, 2014). Pulmonary hypertension is particularly prevalent in CKD patients, with studies reporting a strong association between PH and adverse cardiovascular outcomes (Reque et al, 2016). While right heart catheterization remains the gold standard for diagnosing PH, its invasive nature and limited accessibility make echocardiographic alternatives, such as pPTT, increasingly valuable in clinical practice (Ambroz et al, 2020). Our study is the first to show that PON1 is independently associated with pPTT, suggesting that oxidative stress modulation by PON1 may influence pulmonary vascular function in hemodialysis patients.

An additional noteworthy finding of this study was the positive correlation between post-hemodialysis PON1 activity and early diastolic mitral annular velocity (E'), a recognized marker of left ventricular diastolic function. Reduced E' values are commonly observed in hemodialysis patients (Wang et al., 2021). Considering the established role of oxidative stress in myocardial remodeling and functional impairment, this association implies that PON1 may contribute to cardioprotection in this patient group by counteracting oxidative injury in cardiac tissue. This interpretation is supported by animal research indicating that PON1 deficiency accelerates the progression of atherosclerosis, myocardial fibrosis, and ventricular dysfunction (Gungor et al., 2011; Shih et al., 2000).

Furthermore, our multiple linear regression analysis identified pPTT as an independent predictor of PON1 activity, while C-reactive protein (CRP) approached statistical significance. These results highlight the interrelationship between oxidative stress and systemic inflammation in the

pathophysiology of cardiovascular and vascular alterations in chronic kidney disease. The near-significant association with CRP aligns with previous studies showing an inverse relationship between PON1 activity and inflammatory markers in CKD (Efe et al., 2016), suggesting that therapeutic strategies aimed at enhancing PON1 activity could offer potential benefits for cardiovascular risk reduction in this population.

A major strength of this study is its novelty in demonstrating an independent association between PON1 activity and pPTT, providing new insights into the potential role of antioxidant enzymes in pulmonary vascular dysfunction among hemodialysis patients. The use of paired pre- and post-hemodialysis measurements also strengthens the reliability of our findings by allowing for a direct assessment of hemodialysis-related changes in PON1 activity and echocardiographic parameters.

However, certain limitations should be acknowledged. First, the relatively small sample size may limit the generalizability of our findings. A larger, multicenter study would be beneficial to validate these results and further explore the clinical significance of the observed associations. Second, the absence of a control group prevents direct comparisons with non-hemodialysis populations. Future studies incorporating control groups with both healthy individuals and non-dialysis CKD patients would help clarify whether the observed PON1 alterations are specific to hemodialysis or reflective of CKD pathophysiology in general. While pPTT serves as a valuable echocardiographic marker for pulmonary hypertension (PH) and pulmonary fibrosis (PF), it is important to note that right heart catheterization was not conducted to confirm the pulmonary pressures. Future research integrating both invasive and non-invasive hemodynamic assessments would enhance the clinical applicability of our findings.

This study is the first to report an independent association between PON1 activity and pPTT, a non-invasive marker of pulmonary hypertension and fibrosis in hemodialysis patients. Our findings suggest that PON1 may play a protective role in pulmonary vascular function, potentially mitigating oxidative stress-related endothelial dysfunction. Furthermore, the observed positive correlation between PON1 and E′ highlights a possible link between antioxidant enzyme activity and left ventricular function in hemodialysis patients. These results provide a foundation for future research exploring the therapeutic potential of PON1 modulation in CKD-related cardiovascular and pulmonary complications.

Further studies with larger sample sizes, control groups, and comprehensive hemodynamic assessments are warranted to validate these findings and explore the mechanistic pathways underlying the relationship between PON1, pulmonary vascular function, and cardiac remodeling in CKD.

This study provides novel evidence of an independent association between paraoxonase 1 (PON1) activity and pulmonary pulse transit time (pPTT) in patients undergoing maintenance hemodialysis. As pPTT serves as a non-invasive marker for pulmonary hypertension (PH) and pulmonary fibrosis (PF), our findings suggest that PON1 may play a protective role in pulmonary vascular function by counteracting oxidative stress and inflammation. The observed inverse correlation between PON1 and pPTT reinforces the concept that oxidative stress contributes to pulmonary vascular pathology in hemodialysis patients.

Additionally, our findings demonstrate a significant increase in PON1 activity following hemodialysis, supporting previous reports that dialysis may transiently enhance antioxidant defense mechanisms by reducing the oxidative burden. Furthermore, the positive correlation between post-hemodialysis PON1 levels and early diastolic mitral annular velocity (E′) suggests a potential link between antioxidant

enzyme activity and cardiac function. These results provide a new perspective on the interplay between oxidative stress, cardiovascular dysfunction, and pulmonary hemodynamics in hemodialysis patients.

Given the high prevalence of pulmonary hypertension and cardiovascular complications in chronic kidney disease (CKD) and hemodialysis patients, understanding the role of antioxidant enzymes such as PON1 may offer new therapeutic insights. Future research should focus on elucidating the mechanistic pathways underlying the relationship between PON1 activity, oxidative stress, and pulmonary vascular function. Additionally, interventional studies examining strategies to enhance PON1 activity—either through pharmacological agents, dietary modifications, or novel therapeutic approaches—could provide valuable information on potential protective interventions for CKD-related cardiovascular and pulmonary complications.

While our findings provide important insights, they should be interpreted considering the study's limitations. The small sample size and lack of a non-hemodialysis control group limit the generalizability of our results. Future studies incorporating larger cohorts and comparative groups, including non-dialysis CKD patients and healthy individuals, would allow for a more comprehensive evaluation of PON1 dynamics in different patient populations. Furthermore, integrating invasive hemodynamic assessments such as right heart catheterization alongside echocardiographic measurements would help validate the clinical relevance of pPTT as a surrogate marker for pulmonary hypertension.

In conclusion, our study is the first to report an independent association between PON1 activity and pPTT in hemodialysis patients, highlighting a potential antioxidant-mediated protective mechanism in pulmonary and cardiovascular function. These findings underscore the importance of oxidative stress modulation in CKD and its potential impact on pulmonary hypertension and diastolic dysfunction. Future research should further explore the therapeutic implications of PON1 modulation, with the aim of improving cardiovascular and pulmonary outcomes in hemodialysis patients.

Conflict of Interest

The authors declare that there are no conflicts of interest with other persons or organizations related to this article.

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