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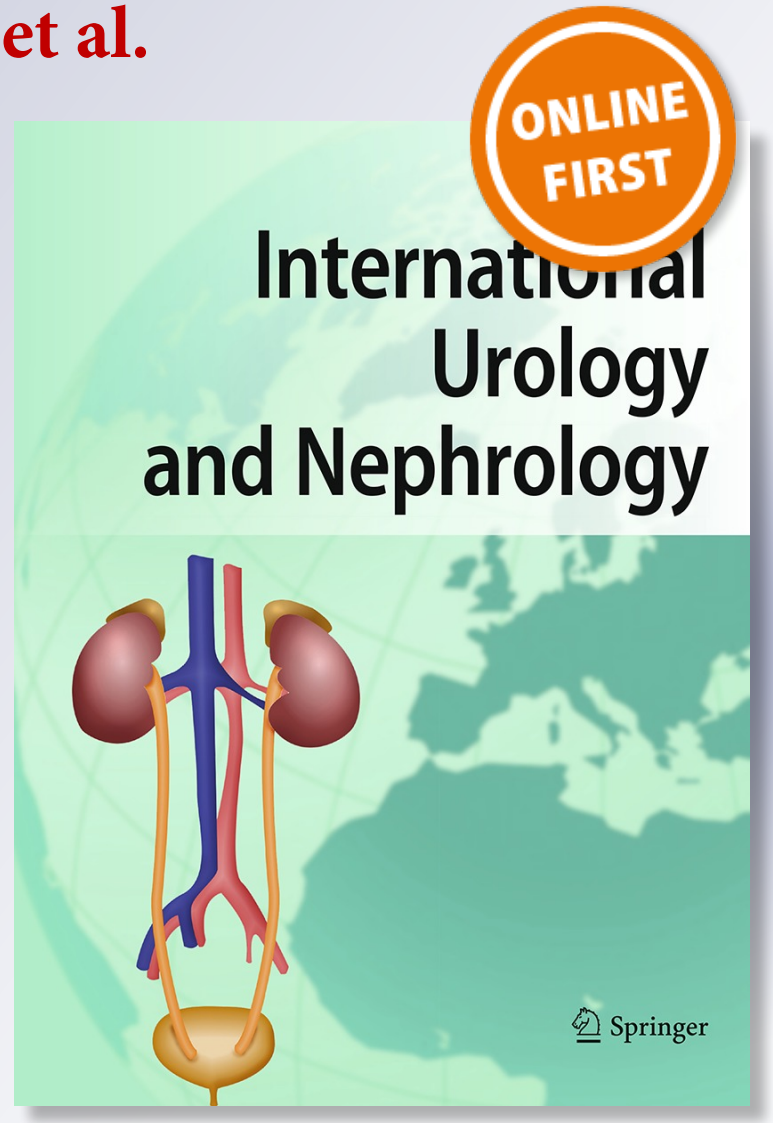


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NEPHROLOGY - ORIGINAL PAPER

# Serum paraoxonase activity is associated with epicardial fat tissue in renal transplant recipients

**Eray Eroglu[1] · Ismail Kocyigit[2] · Aydin Unal[2] · Hafsa Korkar[1] · Cigdem Karakukcu[3] · Ozcan Orscelik[4] · Murat Hayri Sipahioglu[2] · Bulent Tokgoz[2] · Oktay Oymak[2]**

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**Abstract**
*Aims* Cardiovascular disease is a major cause of mortality in renal transplant recipients. Paraoxonase-1 (PON-1) has been shown to protect against atherosclerosis by modifying lipoproteins. Epicardial fat tissue (EFT) has been proposed as a new cardiovascular risk factor. The aim of this study was to investigate the relationship between PON-1 activity and EFT in renal transplant recipients.
*Methods* Eighty renal transplant recipients were enrolled in this cross-sectional study. PON-1 activity was assessed from the rate of enzymatic hydrolysis of paraoxon to *p*-nitrophenol. EFT was measured by echocardiography.
*Results* The mean age of the patients was 40.4 ± 12.3 years and mean post transplant follow-up duration was 57.2 ± 46 months. Mean PON-1 activity was 68.5 ± 30 U/L. PON-1 activity was positively correlated with age and body mass index and negatively correlated with parathyroid hormone, dialysis duration and EFT. The mean EFT thickness was 0.64 ± 0.17 cm. Multiple linear regression analysis was used to define independent determinants of EFT in renal transplant recipients. According to linear regression analysis, PON-1 levels and age were found to be independent predictors of EFT.
*Conclusion* Reduced PON-1 activity was negatively associated with EFT and PON-1 activity independently predicts EFT in renal transplant recipients.

**Keywords** Paraoxonase · Cardiovascular risk · Renal transplantation

## Introduction

Cardiovascular disease (CVD) is the main cause of mortality among renal transplant (RT) recipients [1]. This risk is attributed to the presence of end-stage renal disease before transplantation and immunosuppressive treatment after transplantation [2]. However, arterial stiffness, a CVD risk factor, improves after kidney transplantation; however, the leading cause of death in RT recipients is still CVD [3, 4]. Several factors including age, gender, graft function, blood pressure and also donor's age are associated with cardiovascular risk in RT recipients [5, 6].

Paraoxonase-1 (PON-1) is a 354 amino-acid protein with a molecular mass of 43 kDa. PON-1 protects lipids in lipoproteins, macrophages and erythrocytes from oxidation; therefore, it can be a potential contributing factor in preventing atherosclerosis [7]. It has been shown that decreased PON-1 activity is associated with increased cardiovascular risk [8]. PON-1 activity was found to be lower in patients with ESRD and was also restored by renal transplantation [9]. In recent studies, authors have demonstrated the relationship between PON-1 and CVD in renal transplant recipients [10, 11].

Epicardial fat tissue (EFT) is the visceral adipose tissue surrounding the subepicardial coronary vessels and has the

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same origin as abdominal fat tissue. EFT secretes proatherosclerotic and proinflammatory cytokines [12, 13]. It has been well established that EFT is a predictor of CVD in both non uremic and uremic populations, such as in peritoneal dialysis (PD) and hemodialysis (HD) patients [14–16]. However, only one study mentioned that EFT is lower in RT recipients compared to HD patients [17]. At present there are not enough data about EFT and cardiovascular disease in RT recipients.

Thus, we aimed to investigate the relationship between PON-1 and EFT thickness in RT recipients.

## Material and methods

### Study population

This single-center, cross-sectional study was performed in monitored patients with RT at the Nephrology Department of the Medical Faculty of Erciyes University, Turkey, in the period between March 2014 and October 2014. The study was approved by the University Ethics Committee. All participants provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki.

In our tertiary medical center 125 RT recipients are currently being followed up. The patients included in the study were selected according to the following inclusion and exclusion criteria. RT patients were included if they underwent transplantation at least 6 months previously and their serum creatinine level was lower than 1.5 mg/dL. Patients with conditions that could possibly affect EFT thickness were excluded. The exclusion criteria were heart failure, active infection, autoimmune disease, chronic inflammatory diseases and secondary hyperparathyroidism, RT recipients with a serum creatinine level >1.5 mg/dL, and proteinuria at the nephrotic level.

### Biochemical measurements

Blood samples were taken from the vein of the antecubital fossa, with subjects in a seated position and following a 20 min. rest following 12 h of fasting. Glucose, creatinine, and lipid profile were determined using standard methods [18]. C-reactive protein (CRP) was measured using a BN2 model nephelometer (Dade-Behring, Germany) [19]. Tri-potassium EDTA based anticoagulated blood samples were drawn to measure complete blood count (Sysmex K-1000 auto analyzer, Block Scientific, USA) within 30 min of sampling [20].

The basal activity of paraoxonase was measured. Paraoxon is a toxic organophosphate that is also known as diethyl-p-nitrophenylphosphate. PON1 activity was measured in serum samples by Rel Assay Diagnostics®Kit(Turkey). The linear increase of the absorbance of *p*-nitrophenol, which is produced from paraoxon, is followed at kinetic measurement mode. Nonenzymatic hydrolysis of paraoxon was substracted from the total rate of hydrolysis. The molar absorptivity of *p*-nitrophenol is 18.290 $m^{-1}$ $cm^{-1}$ (MK dan 18290/mol/cm) and one unit of paraoxonase activity is equal to 1 μmol of paraoxon hydrolyzed per liter per minute at 37 °C. The reaction was initiated at 37 °C by the addition of the substrate solution, and, by using a spectrophotometer, absorbance was continuously monitored at 405 nm and 25 °C [21].

### Echocardiogram and epicardial fat tissue thickness measurement

All participants underwent transthoracic echocardiography imagings using an echocardiograph equipped with a broadband transducer (Vivid S6, GE Medical Systems, USA). Measurements were obtained from the long axis and apical four-chamber view according to the standard criteria. The echocardiographic images were entered into a computerized database (EchoPac system). The offline measurements of the EFT were performed by two cardiologists blinded to the subjects' information in order to avoid inter-reader variability. The echocardiograms of 20 patients were randomly selected and a second measurement of the EFT was performed 2 weeks later in order to assess the inter-observer and intra-observer variability. Echocardiographic assessments of the EFT were measured according to the method previously described by Iacobellis et al. [22]. The epicardial fat was identified as an echo-free space in the pericardial layers on two-dimensional echocardiography [23, 24]. The maximum EFT was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus as the anatomic landmark at end-diastole in three cardiac cycles. The inter-observer and intra-observer variabilities of the EFT were found as 3.5 and 2.9 %, respectively.

### Statistical analysis

All parameters are expressed as the mean ± SD. A $P$ value <0.05 was considered as significant. Pearson's rank correlation was used to compare correlations of PON-1 and EFT with other variables. Multivariate linear regression analysis was used to study the predictive factors for PON-1 and EFT. All statistical analyses were performed using SPSS, version 15.0 (Chicago, IL, USA).

## Results

The demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. The

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mean age of the patients was 40.4 ± 12.3 years and mean dialysis duration prior to renal transplantation was 47.4 ± 40.1 months. Mean post transplant follow-up duration was 57.2 ± 46 months. Twenty-five patients were on mammalian target of rapamycin (mTOR) inhibitors (10 everolimus, 15 sirolimus), 55 patients were on calcineurin inhibitors (CNIs) (20 cyclosporin A, 35 tacrolimus), and 90 % of patients were taking anti-hypertensive medication. There is no difference between patients treated by mTOR inhibitors and CNIs in terms of EFT (*p*: 0.23) and PON-1 activity (*p*: 0.18).

**Table 1** Demographical, clinical and laboratory characteristics of the study population

| Variables | Mean ± SD |
|---|---|
| Age (years) | 40.4 ± 12.3 |
| Sex (male, %) | 44, 55 % |
| Posttransplantation month | 57.2 ± 46 |
| Dialysis duration (months) | 47.4 ± 40.1 |
| Systolic blood pressure (mmHg) | 132.6 ± 27.3 |
| Diastolic blood pressure (mmHg) | 87.7 ± 22.2 |
| BMI, kg/m$^2$ | 25.3 ± 3.3 |
| BUN (mg/dL) | 19.2 ± 11.4 |
| Creatinine (mg/dL) | 1.2 ± 0.4 |
| Parathyroid hormone (pg/mL) | 67.2 ± 80.2 |
| Uric acid (mg/dL) | 6.3 ± 1.8 |
| Calcium (mg/dL) | 9.6 ± 0.5 |
| Hemoglobin (g/L) | 13.3 ± 1.9 |
| hs-CRP (mg/L) | 6.8 ± 6.7 |
| PON 1 (U/L) | 68.5 ± 30 |
| PON-1 in patients treated by CNIs (U/L) | 67.5 ± 27 |
| PON-1 in patients treated by mTORi (U/L) | 69.1 ± 29 |
| EFTT (cm) | 0.64 ± 0.17 |
| EFTT in patients treated by CNIs (cm) | 0.66 ± 0.14 |
| EFTT in patients treated by mTORi (cm) | 0.63 ± 0.12 |
| Total cholesterol (mg/dL) | 188.7 ± 28.5 |
| HDL-cholesterol (mg/dL) | 38.7 ± 8.2 |
| LDL-cholesterol (mg/dL) | 123.4 ± 26.2 |
| Plasma triglyceride (mg/dL) | 154.7 ± 62.2 |
| Statin usage (*n*, %) | 9 (11) |
| Serum glucose (md/dL) | 106 ± 37 |
| Hemoglobin A1c (%) | 6,4 ± 1.3 |
| Cause of end stage renal disease (*n*, %) | |
| Diabetes mellitus | 15 (19 %) |
| Hypertension | 18 (23 %) |
| Glomerulonephritis | 8 (10 %) |
| Polycystic kidney disease | 3 (4 %) |
| Obstructive uropathy | 9 (11 %) |
| Unknown | 25 (31 %) |
| Alport syndrome | 1 (1 %) |
| Hellp syndrome | 1 (1 %) |

*BMI* body mass-index, *BUN* blood urea nitrogen, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CNIs* calcineurin inhibitors, *hs-CRP* high selective C-reactive protein, *mTORi* mammalian target of rapamycin inhibitors, *PON-1* paraoxonase-1, *EFTT* epicardial fat tissue thickness

Mean PON-1 activity was 68.5 ± 30 U/L. PON-1 activity was negatively correlated with EFT (*r*: −0.27, *p*: 0.01) (Fig. 1), dialysis duration (*r*: −0.24, *p*: 0.04) (Fig. 2), and parathyroid hormone (*r*: −0.28, *p*: 0.03) (Fig. 3) and positively correlated with age (*r*: 0.36, *p*: 0.01) and body mass index (*r*: 0.40, *p*: 0.01; Table 2). The mean EFT thickness was 0.64 ± 0.17 cm. Multiple linear regression analysis was used to define independent determinants of EFT in renal transplant recipients. According to linear regression

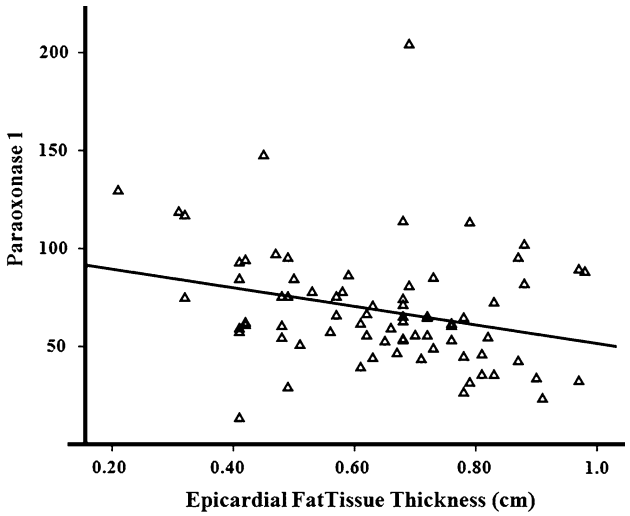


**Fig. 1** Correlation analysis of PON-1 and EFT

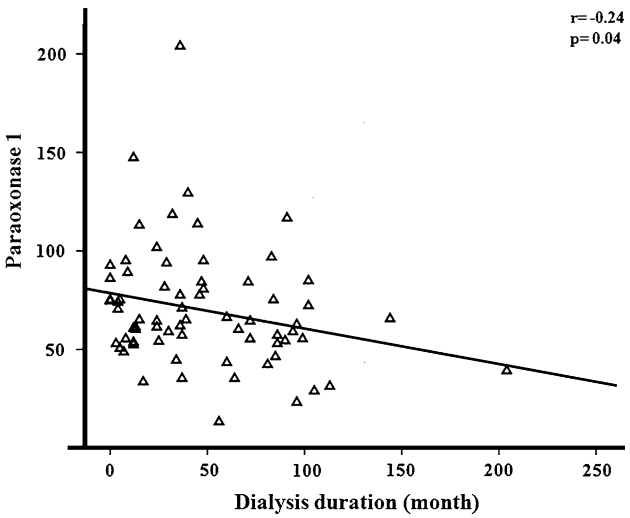


**Fig. 2** Correlation analysis of PON-1 and dialysis duration

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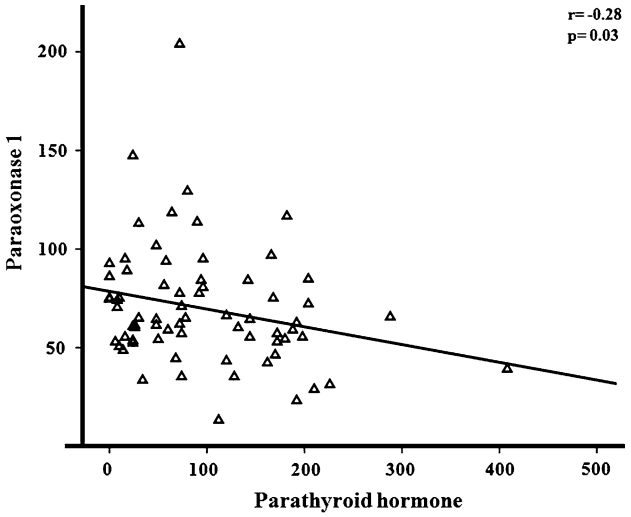


**Fig. 3** Correlation analysis of PON-1 and parathyroid hormone

**Table 2** Correlation analysis of PON-1 with other variables

| | PON 1 | | |
|---|---|---|---|
| | rho | *p* value | 95 % confidence interval |
| Age | 0.36 | 0.01 | (−0.16 to 0.32) |
| Parathyroid hormone | −0.28 | 0.03 | (−0.30 to 0.86) |
| Dialysis duration | −0.24 | 0.04 | (−0.22 to 0.21) |
| EFTT | −0.29 | 0.01 | (−0.42 to 0.15) |
| BMI | 0.40 | 0.01 | (−0.26 to 0.22) |

*EFTT* epicardial fat tissue thickness, *BMI* body-mass index

**Table 3** Multivariate linear regression analysis of the predictive factors for EFTT ($r^2 = 0.282$)

| Variables | $\beta$ | *p* | 95 % confidence interval |
|---|---|---|---|
| Parathyroid hormone | −0.12 | 0.12 | 0.3 (−0.23 to 0.7) |
| Dialysis duration | −0.24 | 0.08 | 0.4 (−0.20 to 0.6) |
| PON 1 | −0.26 | 0.04 | 0.6 (−0.2 to 0.9) |
| Age | 0.31 | 0.02 | 0.8 (−0.1 to 0.9) |

*PON-1* paraoxonase -1, *EFTT* epicardial fat tissue thickness

analysis, PON-1 levels and age were found independent predictors of EFT (Table 3).

## Discussion

Cardiovascular disease is the main cause of death in renal transplant recipients, as in patients with end-stage renal disease. The presence of atherosclerosis due to traditional risk factors including hypertension, diabetes, and hyperlipidemia and also non-traditional risk factors such as oxidative stress is attributed to increased CVD risk in RT patients [1, 2, 25]. PON-1 is an enyzme that protects against atherosclerosis by preventing lipid oxidation and its level is decreased in chronic kidney disease [9, 10]. EFT is a kind of adipose tissue which is similar to abdominal visceral fat and it is closely linked to CVD [14]. It has been previously shown that PON-1 is associated with arterial stiffness in RT patients; however, the data about PON-1 and EFT are lacking in this population [11]. Thus, according to the best of our knowledge, we have demonstrated herein, for the first time, that PON-1 activity is associated with EFT and also independently predicts EFT in RT recipients as a major finding of our study. Another important result of this study is that PON-1 levels are negatively correlated with dialysis duration before renal transplantation.

Oxidative stress is closely linked to vascular dysfunction and the balance between oxidant and anti-oxidant mechanisms is relevant to the occurrence of atherosclerosis. Oxidized low-density lipoprotein (LDL) contributes to atherosclerosis. Moreover, high-density lipoprotein (HDL) plays a crucial role in the prevention of atherosclerosis by protecting LDL from oxidation [26, 27]. PON-1 is an enzyme that is synthesized in the liver and secreted to the blood. However PON-1 is involved in many enyzmatic activities, such as arylesterase and lactonase. Its main function is its binding to HDL and protecting LDL from lipid peroxidation [28]. Moreover, an inverse association was demonstrated between oxidative stress and PON-1 as a potent HDL-associated antioxidant enzyme [29]. Decreased PON-1 activity has been reported in populations with high cardiovascular risk including diabetes mellitus, coronary artery disease, and chronic kidney disease [9, 30, 31]. The role of PON-1 in cardiovascular risk in RT recipients has not been widely studied; thus recent studies have focused on this relation. Hasselwander et al. [32] demonstrated that PON-1 gene polymorphisms and enzyme activity are not associated with increased cardiovascular risk. Supporting these findings, Dantoine et al. [9] showed that the PON-1 activity of RT patients was similar to that of control subjects and they reported that renal transplantation restored PON-1 activity. In contrast to these studies, Paragh et al. [33] found that PON-1 activity was decreased in RT recipients. Also, Sztanek et al. reported that PON-1 activity is associated with increased CVD risk in RT patients [10]. More recently, Gungor et al. [11] found that there was a correlation between PON-1 level and atherosclerosis in RT recipients.

A recently defined cardiovscular risk factor is EFT, which is located subepicardially around both ventricles of the heart. EFT is a metabolically active organ that secretes many cytokines like TNF-a, IL-6, angiotensinogen and plasminogen activator inhibitor-1 (PAI-1), which are proinflammatory or proatherogenic [34]. According

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to these findings, recent interest has shifted towards the role of EFT in CVD in both renal and non-renal patients. Increased EFT thickness, as obtained by echocardiography, is related with atherosclerosis in patients with diabetes and also hypertension [35, 36]. Turkmen et al. [37] found that that EFT was increased in ESRD patients and a positive correlation between EFT and malnutrition-inflammation-atherosclerosis syndrome was revealed in their study. They also reported in another study that EFT was associated with coronary artery calcification in PD patients [16]. Moreover, a recent study in HD patients implicated that EFT predicts mortality in HD patients [38]. After the suggestion of EFT use in the prediction of CVD risk assessment, Karohl et al. [39] reported that EFT may be useful and correlated with myocardial perfusion for screening CKD patients prior to renal transplantation in order to predict future cardiovascular risk. Only one report by Colak et al. [17] assessed the role of EFT in renal transplant patients and they concluded that EFT is correlated with left ventricle mass index. In addition, they observed that EFT thickness was similar to that in a healthy population and significantly lower than that of HD patients in their cohort. However, data on PON-1 and EFT are lacking in renal transplant recipients. The role of oxidative stress and its association with CVD risk stratification remains unclear. Our study showed that PON-1 activity was inversely correlated with EFT and that PON-1 is one of the independent predictors of EFT in renal transplant recipients.

The present study has several limitations. Firstly, it is a cross-sectional study. Secondly, only a small number of patients were enrolled in the investigation due to its single-center study design. Thus, prospective studies are needed in larger populations. Thirdly, although we found an inverse correlation between PON-1 level and EFT, the pathophysiologic mechanism is unclear. Fourthly, correlations with PON-1 and other variables found were significant, but essentially weak (rho <0.3 except age and BMI). Finally, we assessed EFT thickness by echocardiography. Although magnetic resonance imaging and computerized tomography may be more accurate due to volumetric measurement availability, echocardiography has several advantages in that it is easily accessible, has a low cost and does not require X-ray exposure.

In conclusion, PON-1 activity is associated with EFT in renal transplant recipients. PON-1 might be useful in the assessment of oxidative status in RT recipients. Finally, our results should be interpreted with caution. Further studies are needed to validate these results.

#### Compliace with Ethical Standards

**Conflict of interest** The authors declare that there is no conflict of interest.

## References


1. Lentine KL, Hurst FP, Jindal RM, Villines TC, Kunz JS, Yuan CM, Hauptman PJ, Abbott KC (2010) Cardiovascular risk assessment among potential kidney transplant candidates: approaches and controversies. Am J Kidney Dis 55(1):152–167
2. Ghanta M, Kozicky M, Jim B (2015) Pathophysiologic and treatment strategies for cardiovascular disease in end-stage renal disease and kidney transplantations. Cardiol Rev 23(3):109–118
3. Hotta K, Harada H, Sasaki H, Iwami D, Fukuzawa N, Morita K, Seki T, Togashi M, Nonomura K (2012) Successful kidney transplantation ameliorates arterial stiffness in end-stage renal disease patients. Transplant Proc 44(3):684–686
4. Stompór T, Rajzer M, Kawecka-Jaszcz K, Dembińska-Kieć A, Janda K, Wójcik K, Tabor B, Zdzienicka A, Grzybowska EJ, Sulowicz W (2005) Renal transplantation ameliorates the progression of arterial stiffness in patients treated with peritoneal dialysis. Perit Dial Int 25(5):492–496
5. Delahousse M, Chaignon M, Mesnard L, Boutouyrie P, Safar ME, Lebret T, Pastural-Thaunat M, Tricot L, Kolko-Labadens A, Karras A, Haymann JP (2008) Aortic stiffness of kidney transplant recipients correlates with donor age. J Am Soc Nephrol 19(4):798–805
6. Kneifel M, Scholze A, Burkert A, Offermann G, Rothermund L, Zidek W, Tepel M (2006) Impaired renal allograft function is associated with increased arterial stiffness in renal transplant recipients. Am J Transplant 6(7):1624–1630
7. Rosenblat M, Volkova N, Aviram M (2011) Injection of paraoxonase 1 (PON1) to mice stimulates their HDL and macrophage antiatherogenicity. Biofactors 37(6):462–467
8. Tang WH, Hartiala J, Fan Y, Wu Y, Stewart AF, Erdmann J, Kathiresan S, CARDIoGRAM Consortium, Roberts R, McPherson R, Allayee H, Hazen SL (2012) Clinical and genetic association of serum paraoxonase and arylesterase activities with cardiovascular risk. Arterioscler Thromb Vasc Biol 32(11):2803–2812
9. Dantoine TF, Debord J, Charmes JP, Merle L, Marquet P, Lachatre G, Leroux-Robert C (1998) Decrease of serum paraoxonase activity in chronic renal failure. J Am Soc Nephrol 9(11):2082–2088
10. Sztanek F, Seres I, Harangi M, Lőcsey L, Padra J, Paragh GJ, Asztalos L, Paragh G (2012) Decreased paraoxonase 1 (PON1) lactonase activity in hemodialyzed and renal transplanted patients. A novel cardiovascular biomarker in end-stage renal disease. Nephrol Dial Transplant 27(7):2866–2872
11. Gungor O, Kismali E, Sisman AR, Kircelli F, Asci G, Topal K, Sipahi S, Tuncel P, Ozkahya M, Toz H (2013) The associations between serum paraoxonase 1 activity and carotid atherosclerosis in renal transplant patients. Clin Nephrol 80(3):198–202
12. Iacobellis G, Corradi D, Sharma AM (2005) Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2(10):536–543
13. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y (2003) Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 108(20):2460–2466
14. Katsiki N, Mikhailidis DP, Wierzbicki AS (2013) Epicardial fat and vascular risk: a narrative review. Curr Opin Cardiol 28(4):458–463
15. Turan MN, Gungor O, Asci G, Kircelli F, Acar T, Yaprak M, Ceylan N, Demirci MS, Bayraktaroglu S, Toz H, Ozkahya M, Ok E (2013) Epicardial adipose tissue volume and cardiovascular disease in hemodialysis patients. Atherosclerosis 226(1):129–133

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16. Turkmen K, Ozbek O, Kayrak M, Samur C, Guler I, Tonbul HZ (2013) Peri-aortic fat tissue thickness in peritoneal dialysis patients. Perit Dial Int 33(3):316–324
17. Colak H, Kilicarslan B, Tekce H, Tanrisev M, Tugmen C, Aktas G, Kursat S (2015) Relationship between epicardial adipose tissue, inflammation and volume markers in hemodialysis and transplant patients. Ther Apher Dial 19(1):56–62
18. Burtis CA, Ashwood ER. (1994) Tietz textbook of clinical chemistry, ed 2, Philadelphia, WB Saunders
19. Lolekha PH, Chittamma A, Roberts WL, Sritara P, Cheepudomwit S, Suriyawongpaisal P (2005) Comparative study of two automated high-sensitivity C-reactive protein methods in a large population. Clin Biochem 38(1):31–35
20. Gutiérrez G, Jou JM, Carlos Reverter J, Martínez-Brotons F, Domingo A, Antonio Iriarte J, Remacha A, Rey J, Vives Corrons JL (1996) standardization committee for haematology. External quality assurance program for general hematology. Evaluation of the 1994 results. Sangre (Barc) 41(2):115–123
21. Reiner E, Svedruzic D, Simeon-Rudolf V, Lipovac V, Gavella M, Mrzljak V (1999) Paraoxonase and arylesterase activities in the serum of two hyperlipoproteinaemic patients after repeated extracorporal lipid precipitation. Chem Biol Interact 14(119–120):405–411
22. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, Leonetti F (2003) Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 11:304–310
23. Silaghi AC, Poant L, Valea A, Pais R, Silaghi H (2011) Is epicardial adipose tissue, assessed by echocardiography, a reliable method for visceral adipose tissue prediction? Med Ultrason 13:15–20
24. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F (2003) Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 88:5163–5168
25. Kasiske BL (1988) Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med 84(6):985–992
26. Miller NE (1987) Associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis. Am Heart J 113(2 Pt 2):589–597
27. Parthasarathy S, Barnett J, Fong LG (1990) High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochim Biophys Acta 1044(2):275–283
28. Draganov DI, La Du BN (2004) Pharmacogenetics of paraoxonases: a brief review. Naunyn Schmiedebergs Arch Pharmacol 369(1):78–88
29. Bełtowski J, Wójcicka G, Jamroz A (2003) Leptin decreases plasma paraoxonase 1 (PON1) activity and induces oxidative stress: the possible novel mechanism for proatherogenic effect of chronic hyperleptinemia. Atherosclerosis 170(1):21–29
30. Patra SK, Singh K, Singh R (2013) Paraoxonase 1: a better atherosclerotic risk predictor than HDL in type 2 diabetes mellitus. Diabetes Metab Syndr 7(2):108–111
31. Mackness MI, Mackness B, Durrington PN (2002) Paraoxonase and coronary heart disease. Atheroscler Suppl 3(4):49–55
32. Hasselwander O, Savage DA, McMaster D, Loughrey CM, McNamee PT, Middleton D, Nicholls DP, Maxwell AP, Young IS (1999) Paraoxonase polymorphisms are not associated with cardiovascular risk in renal transplant recipients. Kidney Int 56(1):289–298
33. Paragh G, Asztalos L, Seres I, Balogh Z, Löcsey L, Kárpáti I, Mátyus J, Katona E, Harangi M, Kakuk G (1999) Serum paraoxonase activity changes in uremic and kidney-transplanted patients. Nephron 83(2):126–131
34. Iacobellis G, Bianco AC (2011) Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 22:450–457
35. Cetin M, Cakici M, Polat M, Suner A, Zencir C, Ardic I (2013) Relation of epicardial fat thickness with carotid intima-media thickness in patients with type 2 diabetes mellitus. Int J Endocrinol 2013:769175
36. Natale F, Tedesco MA, Mocerino R, de Simone V, Di Marco GM, Aronne L, Credendino M, Siniscalchi C, Calabrò P, Cotrufo M, Calabrò R (2009) Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. Eur J Echocardiogr 10(4):549–555
37. Turkmen K, Kayikcioglu H, Ozbek O, Solak Y, Kayrak M, Samur C, Anil M, Zeki Tonbul H (2011) The relationship between epicardial adipose tissue and malnutrition, inflammation, atherosclerosis/calcification syndrome in ESRD patients. Clin J Am Soc Nephrol 6(8):1920–1925
38. D'Marco LG, Bellasi A, Kim S, Chen Z, Block GA, Raggi P (2013) Epicardial adipose tissue predicts mortality in incident hemodialysis patients: a substudy of the Renagel in New Dialysis trial. Nephrol Dial Transplant 28(10):2586–2595
39. Karohl C, D'Marco L, Bellasi A, Raggi P (2013) Hybrid myocardial imaging for risk stratification prior to kidney transplantation: added value of coronary calcium and epicardial adipose tissue. J Nucl Cardiol 20(6):1013–1020