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Epicardial adipose tissue volume and cardiovascular disease in hemodialysis patients

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ABSTRACT

Objective: Epicardial adipose tissue (EAT) is proposed as a cardiovascular risk marker in non-uremic subjects. However, little is known about its role in patients with higher cardiovascular risk profile such as chronic kidney disease. The aim of this study was to investigate the relationship between EAT and several cardiovascular surrogate markers (coronary artery calcification (CAC), arterial stiffness and atherosclerosis) in patients on maintenance hemodialysis.
Methods: A total of 191 prevalent hemodialysis patients were enrolled in this cross-sectional study. EAT and CAC scores (CACs) were determined by multi-slice computerized tomography, arterial stiffness by carotid-femoral pulse wave velocity (PWV), and carotid artery intima-media thickness (CA-IMT) by B-mode doppler ultrasonography.
Results: Mean age was 59 ± 13 years and time on hemodialysis 75 ± 44 months. Twenty percent of the patients had diabetes. Mean EAT volume was 62.6 ± 26.8 cm^3/m^2. Mean CA-IMT and PWV values increased across the EAT tertiles. EAT was correlated with age, female gender, body mass index, albumin and lipid parameters. Additionally, CA-IMT and PWV values were positively correlated with EAT. EAT volume was significantly higher in patients with CACs >10 compared to the patients with CACs ≤10. Despite the univariate associations between EAT and cardiovascular surrogate markers, only age, body mass index and total cholesterol levels were associated with EAT in adjusted models.
Conclusions: In prevalent hemodialysis patients, EAT is correlated with atherosclerosis, arterial stiffness and the presence of CAC. However, this correlation is not independent of other risk factors.

1. Introduction

Epicardial adipose tissue (EAT) is the visceral adipose tissue surrounding the heart, especially the subepicardial coronary vessels. It has the same origin as abdominal visceral fat, which has been strongly associated with coronary artery disease (CAD). Although, little is known about its physiologic and metabolic roles, EAT has been implicated as a cardiovascular risk factor in non-uremic patients [1]. Recently, it has been shown that EAT can produce and secrete several proatherosclerotic and proinflammatory hormones and cytokines such as TNF-α, IL-6, and adipocytokines that might underlie its association with the presence of CAD [2–5]. Furthermore, this association has been shown to be independent of body mass index and diabetic status [6]. Although EAT volume was significantly associated with atherosclerosis and coronary artery calcification (CAC) in patients without chronic kidney disease in several studies [7–11], some studies could not confirm the relation between EAT and CAD [12]. In a recently published meta-analysis, both EAT thickness and volume was associated with CAD, but not specifically with CAC [13].

In patients with chronic renal disease, inflammatory burden is much more pronounced than the general population suggesting that EAT may end up with more deleterious outcomes. Thus, in a recent study, Turkmen et al. [14] reported higher EAT in dialysis patients compared to healthy controls and a significant association of EAT with malnutrition-inflammation-atherosclerosis-calcification syndrome (MIAC). However, the association between EAT and cardiovascular disease still remains unclear in dialysis patients who have higher cardiovascular risk profile compared to the general population.

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The aim of this study was to investigate the relationships between EAT determined by multi-slice tomography and carotid artery intima-media thickness (CA-IMT), arterial stiffness and coronary artery calcification in hemodialysis (HD) patients.

2. Methods

2.1. Patients

Study group consisted of a subgroup of patients participated in a clinical trial, EGE Study (Clinicaltrials ID NCT00295191). EGE Study was a randomized controlled trial to explore the effects of membrane flux and dialyzate purity on cardiovascular outcomes. Main inclusion criteria were aged 18–80 years and undergoing thrice weekly HD; main exclusion criterion was life expectancy less than a year. Multi-slice computerized tomography, pulse wave analysis and carotid artery ultrasonography were carried out in study participants according to the study protocol.

In this cross-sectional study, we measured EAT in 191 maintenance HD patients who underwent all of three examinations within the period of 3 months, in order to seek whether EAT is associated with CAC score (CACs), arterial stiffness and CA-IMT.

Demographical, clinical and laboratory data were collected from patients' charts. The aetiologies of end-stage renal disease were diabetic nephropathy in 39, chronic glomerulonephritis in 15, chronic pyelonephritis in 14, hypertensive renal disease in 38, polycystic kidney disease in 16, amyloidosis in one and unknown in 68. Eighty-nine percent of the patients were taking calcium-based phosphate binders; the use of vitamin D and anti-hyperlipidemic drugs were 32% and 11%, respectively. All of the patients were on thrice weekly 4-h hemodialysis treatment with standard bicarbonate dialysis (Na 138 mmol/l, K 2.0 mmol/l, Ca 1.5 mmol/l, Mg 0.5 mmol/l, Cl 109 mmol/l, HCO_3 32 mmol/l, acetate 3 mmol/l, glucose 5.5 mmol/l). Sixty-four percent of the patients were dialyzed with a high-flux membrane (FX60/80; Fresenius Medical Care, Bad Homburg, Germany).

Local Ethics Committee approved the study and informed consent was obtained from all patients. The study was performed according to the recommendations of the Declaration of Helsinki.

2.2. Laboratory measurements

Blood samples were collected at the beginning of the HD session under fasting conditions. Until use, all samples were kept at −80 °C. All biochemical parameters were performed by standard auto-analyzers (Architect C8000 and CELL-DYN 3700) in the same central laboratory registered to external quality-control programs.

2.3. Measurement of coronary artery calcification

Multi-slice computerized tomography scans were performed with a 16-slice technique (Aquilion 16, Toshiba Medical Systems, Tokyo, Japan). All scans with slices of 3.0 mm thickness were acquired under the following condition: 250 mA of tube current, 62 mAs effective. Images were obtained during a single breath-hold of 12–15 s. Data obtained during the diastolic phase of the cardiac cycle were used for image reconstruction, with electrocardiography (ECG) monitoring. Calcium scoring was performed on the reconstructed image sets with commercially available software (Terarecon 3.4.2.11, CA, USA). Threshold calcium determination was set using a density of at least 130 Hounsfield units. CACs was calculated by summing the calcification score in the left main, the left anterior descending, the left circumflex and the right coronary artery. CACs was blindly evaluated by the same radiologist, according to the method described by Agatston et al. [15].

2.4. Measurement of epicardial adipose tissue volume

Epicardial adipose tissue was measured from the images of CAC measurements by the following protocol. Computed tomography datasets were transferred to workstation for volume analysis (Advantage Workstation 4.2, GE Healthcare). Epicardial fat was defined as the adipose tissue between the surface of myocardium and the visceral layer of the pericardium (visceral epicardium). Parietal pericardium was manually traced in every third slice starting from the aortic root to the apex. A density range of −190 to −30 Hounsfield units (HU) was used to isolate the adipose tissue [16]. Dedicated software discerned fat from other tissues and measured epicardial fat volume. Measurements of EAT and CACs were evaluated by same radiologist blinded to the study protocol. The intra-observer variability was 0.7%. EAT results were corrected with body surface area.

2.5. Arterial stiffness measurements

Arterial stiffness was measured by the same operator using the Sphygmocor device (AtCor Medical, Sydney, Australia). Carotid-femoral pulse wave velocity (PWV) was measured by sequential recordings of the arterial pressure wave at the carotid and femoral arteries, and by measurement of the distance from the carotid sampling site to the suprasternal notch and from the suprasternal notch to the femoral site. With a simultaneous ECG recording of the *R*-wave as reference, the integral software calculated the pulse wave transit time. The intra-observer variability was 3.5%.

2.6. Carotid artery intima-media thickness measurement

Ultrasonographic studies on common carotid arteries were carried out by gray scale high-resolution color Doppler ultrasound (ATL HDI 5000 scanner Philips, ATL ultrasound, Bothell, WA, ABD) equipped with 5–12 MHz linear transducer. The same operator performed all procedures on both sides of two longitudinal images of the each common carotid artery on the morning. Average of two CA-IMT values from each side were used to calculate mean CA-IMT. Intra-observer coefficient of variation was 2.8%.

2.7. Statistical analysis

All parameters are expressed as mean ± SD. *P* value less than 0.05 was considered as statistically significant. Comparisons between two groups were assessed by independent *t*-test analysis. Differences between more than two groups were analyzed by ANOVA. Spearman's analysis was used to assess correlations of EAT and other variables. Multivariate linear regression analysis was used for independent predictors associated with EAT. Ordinary logistic regression analysis was used to study the predictive factors for the presence of CAC (dichotomized as CACs >10 versus ≤ 10) [17]. For variables associated with CA-IMT and PWV, linear multivariate regression analyses were used. For each examination, only variables found to be significant in univariate analysis were included in multivariate analyses. All statistical analyses were performed using SPSS, version 13.0 (Chicago, IL, USA).

3. Results

The clinical characteristics and laboratory data of the whole study population are summarized in Table 1. Briefly, mean age was 59 ± 13 years and time on HD 75 ± 44 months. Twenty percent of the patients had a history of diabetes and 19% history of CVD. Prevalence of the patients with a body mass index above 25 and 30 kg/m^2 were 33% and 10%, respectively.

Table 1
Comparison of the EAT tertiles and correlation of EAT with other parameters.[a]

	All patients $N = 191$	Low EAT tertile (<46.3 cm^3/m^2) $N = 63$	Middle EAT tertile (46.3–71.2 cm^3/m^2) $N = 64$	High EAT tertile (>71.2 cm^3/m^2) $N = 64$	*P* value	Rho (p)
EAT (cm^3)	107.2 ± 47.4	57.8 ± 15.5	101.9 ± 14.7	161.3 ± 29.9	<0.001	–
EAT/BSA (cm^3/m^2)	62.6 ± 26.8	35.1 ± 8.5	58.5 ± 7.3	93.9 ± 16.4	<0.001	–
Age (years)	59.4 ± 12.9	53.4 ± 14.3	59.0 ± 11.0	65.7 ± 10.2	<0.001	0.42 (<0.001)
Gender (Female,%)	48	46	39	58	0.10	0.15 (0.03)
Diabetes (%)	20	14	27	20	0.23	0.07 (0.31)
CVD history (%)	18	10	20	25	0.07	0.11 (0.10)
Time on HD (month)	75.0 ± 44.6	85 ± 46	76 ± 54	62 ± 24	0.01	−0.16 (0.02)
Body mass index (kg/m^2)	23.7 ± 4.0	22.2 ± 3.5	23.6 ± 3.2	25.4 ± 4.7	0.004	0.26 (0.006)
Albumin (g/dl)	4.05 ± 0.24	4.08 ± 0.27	4.07 ± 0.22	4.01 ± 0.22	0.23	−0.18 (0.01)
Creatinine (mg/dl)	8.8 ± 1.7	9.0 ± 1.9	8.9 ± 1.7	8.5 ± 1.4	0.25	−0.11 (0.13)
Hemoglobin (g/dl)	11.3 ± 1.0	11.3 ± 0.96	11.6 ± 1.0	11.1 ± 0.9	0.02	−0.10 (0.16)
Calcium (mg/dl)	9.0 ± 0.6	9.0 ± 0.6	9.1 ± 0.7	9.0 ± 0.6	0.61	−0.03 (0.65)
Phosphate (mg/dl)	4.7 ± 0.9	4.4 ± 0.8	4.8 ± 0.9	4.8 ± 0.9	0.03	0.10 (0.14)
PTH (pg/ml)	320 ± 273	368 ± 257	276 ± 243	321 ± 338	0.57	−0.17 (0.21)
Hs-CRP (mg/dl)	1.09 ± 1.20	0.96 ± 1.02	1.30 ± 1.55	1.01 ± 0.93	0.24	0.08 (0.23)
Total cholesterol (mg/dl)	171 ± 43	159 ± 36	173 ± 45	179 ± 46	0.03	0.21 (0.003)
Triglyceride (mg/dl)	177 ± 96	146 ± 63	184 ± 95	199 ± 116	0.008	0.20 (0.005)
LDL cholesterol (mg/dl)	103 ± 33	97.2 ± 30.2	105.8 ± 35.0	107.59 ± 33.6	0.20	0.16 (0.02)
HDL cholesterol (mg/dl)	32 ± 8	33 ± 9.	30 ± 7	32 ± 9	0.22	−0.03 (0.62)
CA-IMT (mm)	0.74 ± 0.14	0.68 ± 0.16	0.76 ± 0.14	0.76 ± 0.12	0.004	0.22 (0.001)
CAC score	97 (0–601)	28 (0–364)	212 (6–642)	151 (0.5–865)	0.09	0.13 (0.07)
PWV (m/s)	9.9 ± 3.0	9.1 ± 3.2	10.1 ± 3.0	10.5 ± 2.8	0.04	0.22 (0.002)

EAT: Epicardial adipose tissue, BSA: Body surface area, CVD: Cardiovascular disease, HD: hemodialysis, PTH: Paratyroid hormone, hs-CRP: High-sensitive C-reactive protein, LDL: Low-density lipoprotein, CA-IMT: Carotid artery intima-media thickness, CAC: Coronary artery calcification, PWV: Pulse wave velocity.
[a] All variables were expressed as mean ± standard deviation except CAC score which was expressed as median value with interquartile range.

Mean EAT volume was 62.6 ± 26.8 cm^3/m^2 (107.2 ± 47.4 cm^3). Distribution of EAT of the study population is presented in Fig. 1. Severe CAC (CACs >400) was present in 33.7% of the patients, while 26.1% of the patients had no CAC (CACs = 0). Mean PWV was 9.97 ± 3.05 m/s; mean CA-IMT was 0.74 ± 0.15 mm and frequency of carotid plaques was 47.8% with a mean length 2.00 mm (1.00–4.00 mm).

3.1. Predictors for epicardial adipose tissue

Table 1 shows the clinical and laboratory characteristics of the patients according to the EAT tertiles and univariate correlations of EAT. The patients with higher EAT were older, had shorter HD duration, higher body mass index, phosphate, total cholesterol and triglyceride levels, and lower hemoglobin levels. There was no difference with regard to serum albumin, creatinine and Hs-CRP levels. Mean CA-IMT and PWV values significantly increased across EAT tertiles. Fig. 2 shows the univariate correlations between EAT and CACs, CA-IMT and PWV. EAT was positively correlated with CA-IMT ($r = 0.229$, $p = 0.001$), presence of carotid plaque ($r = 0.152$, $p = 0.03$) and PWV ($r = 0.220$, $p = 0.002$) while the relationship between EAT and CACs had borderline significance ($r = 0.131$, $p = 0.07$). When patients were grouped as having CACs ≤10 versus >10, mean EAT volume was significantly higher in patients having a CACs >10 ($n = 127$) (65.5 ± 26.8 versus 56.9 ± 25.9 cm^3/m^2, $p = 0.03$). EAT volume was not different between patients with and without diabetes (61.9 ± 26.9 versus 66.5 ± 26.2 cm^3/m^2, respectively, $p = 0.31$).

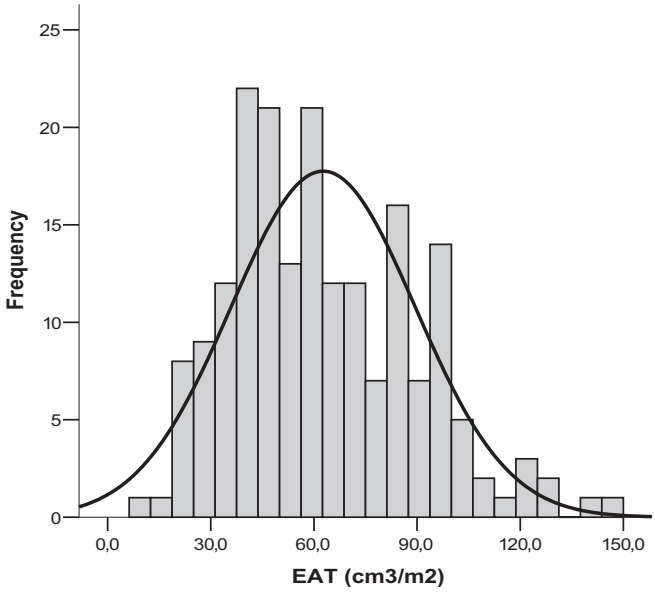

Fig. 1. Distribution of epicardial adipose tissue in the studied population.

Despite univariate associations, EAT volume was not independently associated with CACs, CA-IMT and PWV in adjusted analysis (Table 2). We found that age, body mass index and total cholesterol levels were predictors associated with EAT.

When the patients with known cardiovascular disease history were excluded, EAT was significantly associated with CA-IMT ($r = 0.233$, $p = 0.004$) and PWV ($r = 0.290$, $p < 0.001$) but not CACs ($r = 0.110$, $p = 0.17$) in univariate analysis. In multivariate analysis, EAT was not significantly associated with CA-IMT, PWV and CACs in this subgroup.

We did not find an effect of time on hemodialysis on the association between EAT and atherosclerosis parameters. Also, there was no difference in the association between EAT and CACs, CA-IMT and PWV among the etiologies of end-stage renal disease.

3.2. Predictors of CAC, atherosclerosis and arterial stiffness

In adjusted binary logistic regression analysis, age (RR = 1.09, 95% CI 1.05–1.13, $p < 0.001$), male gender (RR = 2.79, 95% CI 1.30–5.98, $p = 0.008$), presence of diabetes (RR = 7.92, 95% CI 2.18–28.7, $p = 0.002$) and serum phosphate levels (RR = 2.31, 95% CI 1.46–3.65, $p < 0.001$) were independently associated with presence of CAC (Model chi-square: 60.3, $p < 0.001$).

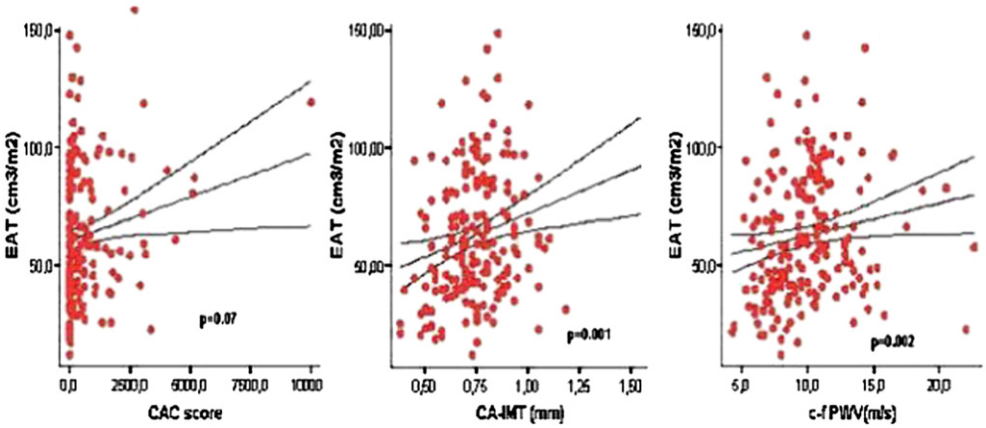

Fig. 2. Correlations of epicardial adipose tissue with coronary artery calcification, atherosclerosis and arterial stiffness.

In multivariate linear regression analysis, age (t = 0.44, $p < 0.001$), presence of diabetes (t: 0.31, $p < 0.001$) and systolic blood pressure (t: 0.28, $p < 0.001$) were predictors for arterial stiffness.

In multivariate linear regression analysis, older age, male gender and presence of diabetes were found as variables associated with CA-IMT (model r^2: 0.38, $p < 0.001$).

4. Discussion

This is the first study investigating the relationship between EAT volume, hypothesized as a cardiovascular risk factor, and several cardiovascular surrogate markers in patients on maintenance HD. Our results show that EAT volume is correlated with carotid artery atherosclerosis and arterial stiffness. While the correlation between CACs and EAT volume is borderline, patients with higher EAT were more likely to develop CAC. However, the associations of EAT with atherosclerosis, arterial stiffness and CACs were not independent of other risk factors in adjusted models.

Arterial stiffness is an important contributor to the increased CV burden. The underlying mechanisms of arterial stiffness are not well defined, but elevated levels of oxidative stress and inflammation, hypervolemia, arterial calcification, activation of the renin–angiotensin–aldosterone system and sympathetic nervous system over-activity are all anticipated to play a role [18,19]. The pathophysiology that links EAT to stiffening is still largely unknown. In the general population, EAT has been showed to be an independent predictor of arterial stiffness [20]. It is suggested that insulin resistance due to accumulation of released fatty acids by lipolysis in liver, pancreas and muscles from the adipocytes and increased levels of proinflammatory cytokines or leptin in the blood may play a role [6]. Regarding the association of EAT with CA-IMT, Natele et al. found that hypertensive patients with echocardiographically determined EAT >7 mm had significantly increased CA-IMT and stiffness parameters compared with those with ≤7 mm [20]. In their study, age, CA-IMT and stiffness parameters were independently associated with EAT. In our study, EAT was correlated with arterial stiffness and CA-IMT. However, this was not independent of other risk factors. Rather, our results showed that conventional risk factors such as age, male gender, presence of diabetes and higher systolic blood pressure levels were strongly risk factors for arterial stiffness and CA-IMT in dialysis patients.

Table 2
The results of stepwise multivariate regression analysis associated with epicardial adipose tissue.

Variable	Standardized coefficients B	t	P value
Model adjusted r^2: 0.38, $p < 0.001$			
Age	0.29	3.0	0.003
Body mass index	0.21	2.57	0.01
Total cholesterol	0.24	2.57	0.01

Included variables in the model were age, gender, time on HD, BMI, serum albumin, total cholesterol, triglyceride, CA-IMT, PWV and CACs.

The association between CAC and EAT is not clear in patients with chronic kidney disease. In our study, EAT was higher in patients with CACs >10 compared to the patients with CACs ≤10. Recently, Turkmen et al. also reported higher EAT volume in peritoneal dialysis patients compared to HD and a significant univariate correlation between EAT and CACs [14]. The same group also reported that peritoneal dialysis patients with a CACs >10 had increased EAT [21]. EAT was found to be increased in the presence of increased MIAC components. EAT was positively correlated with age, body mass index, and presence of MIAC. These parameters were also found as independent predictors of increased EAT. While their primary focus of interest was MIAC, it should be noted that the significance for the correlation between EAT and MIAC was borderline (p = 0.05) and EAT was not corrected for BSA [14]. Vascular calcification in dialysis patients is strongly correlated with calcium-phosphate disturbances. Therefore, arterial media calcification differs in many ways from the atherosclerotic calcification found in non-uremics that might explain the presence of weak correlation between EAT and CACs in dialysis patients.

Epicardial adipose tissue is closely related to visceral adipose tissue rather than the total body fat. Recent studies demonstrated that biological active molecules secreted from EAT such as adipocytokines and inflammatory mediators may have a role in the pathogenesis of atherosclerosis in patients with CAD [4]. Thus, the most possible explanation for the lack of independent association with cardiovascular surrogate markers could be that cellular or biologic functions may be more important than the extent of EAT. Also, both pathophysiological consequences of traditional risk factors and non-traditional risk factors unique to uremic status on cardiovascular system is more pronounced in patients with chronic kidney disease and may have influenced this relation.

Several studies using MSCT demonstrated the association between EAT and traditional risk factors. In a substudy of the Framingham Heart Study, it was shown that pericardial fat was correlated with multiple measures of adiposity and cardiovascular risk factors [22]. In the current study, we found that older age, higher body mass index and total cholesterol levels were independently associated with EAT in hemodialysis patients. The positive association between EAT and the number of metabolic risk factors suggests that EAT might be a valuable quantitative marker of

metabolic impairments and atherosclerosis, and gives us with a clue to risk stratification for coronary artery disease. Additionally, EAT can be obtained from the same scan used to determine CACs, supplementing its appeal for future clinical application.

Our study has several limitations. First, the study was designed as cross-sectional nature and a does not provide a causal link. Additionally, our study was performed in maintenance dialysis. Therefore, there may be a selection bias of including prevalent HD patients (survivors). Furthermore, we cannot rule out a relationship between EAT and cardiovascular surrogate markers in dialysis patients because of inadequate power of studied sample.

As a conclusion, while EAT was correlated with arterial stiffness, CA-IMT and the presence of CAC, this is not independent of other risk factors. Rather, EAT was associated with age, body mass index and total cholesterol levels; well-known traditional risk factors for cardiovascular disease. EAT may indeed not be a cause of but also be a single surrogate marker "on its own" to reflect these cardiovascular disorders. Although there is growing body of evidence that EAT is a new risk marker for the presence of coronary artery disease in general population, it is not known that measurement of EAT can be used to predict or diagnose coronary artery disease instead of MSCT or coronary angiography. However, further large scale clinical and research studies exploring the role of EAT in cardiovascular disease in dialysis population may help us to clarify this issue.

Conflict of interest

EO is a member of scientific board of Fresenius Medical Care, Turkey. The other authors declare no conflict of interest.

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