Original Article

A Low Serum Free Triiodothyronine Level is Associated with Epicardial Adipose Tissue in Peritoneal Dialysis Patients

Ismail Kocyigit[1], Ozkan Gungor[2], Aydin Unal[1], Mustafa Yasan[3], Ozcan Orscelik[3], Onur Tunca[1], Eray Eroglu[4], Murat Hayri Sipahioglu[1], Bulent Tokgoz[1], Ibrahim Ozdogru[3], Ali Dogan[3] and Oktay Oymak[1]

[1]Department of Nephrology, Erciyes University Medical Faculty, Kayseri, Turkey
[2]K.Maras Training and Research Hospital, K.Maras, Turkey
[3]Department of Cardiology, Erciyes University Medical Faculty, Kayseri, Turkey
[4]Department of Internal Medicine, Erciyes University Medical Faculty, Kayseri, Turkey

***Aim*: Cardiovascular disease is a major cause of mortality in dialysis patients. Epicardial adipose tissue (EAT) has been proposed as a cardiovascular risk marker in this population. Subclinical hypothyroidism and low free triiodothyronine (fT3) levels are associated with EAT in patients without chronic renal failure. The aim of this study was to investigate the relationship between EAT and low free T3 levels in peritoneal dialysis (PD) patients.**

***Methods*: A total of 125 prevalent PD patients were enrolled in this cross-sectional study. The epicardial fat thickness (EFT) was measured by echocardiography, and the endothelial function was assessed by flow mediated dilatation (FMD). Thyroid function tests were performed by an enzyme immunoassay.**

***Results*: The mean age of the patients was 51 ± 13, and the time on PD was 36 months. The mean EFT was 6.7 ± 2.9 mm. The EFT correlated positively with the patient age, systolic blood pressure (BP), mean BP, high sensitivity C-reactive protein (hs-CRP) level and body mass index (BMI), and negatively with the fT3 level and FMD. The median fT3 value was 2.53, and patients were divided according to their serum fT3 values (within the normal range and below the reference level). Compared with patients in the low fT_3 group, the subjects in the normal fT3 group had higher serum albumin levels and FMD, but a lower BMI, plasma fasting glucose level, EFT, TSH level, hs-CRP level, low density lipoprotein (LDL) cholesterol level and mean BP in office measurements, and both the diastolic BP and mean BP by ambulatory blood pressure measurement. A multivariate linear regression analysis showed that the EFT was predicted by the hs-CRP and fT_3 levels.**

***Conclusion*: Low free T3 levels are associated with the epicardial fat thickness in PD patients. Further studies are needed to evaluate the pathogenesis and to support these findings.**

J Atheroscler Thromb, 2014; 21:1066-1074.

Key words: Epicardial adipose tissue, Peritoneal dialysis, Free triiodothyronine

Introduction

Cardiovascular (CV) disease is a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). In fact, more than 50% of the deaths among peritoneal dialysis (PD) patients can be attributed to CV disease[1)]. In addition to traditional risk factors, the presence of uremic toxins, anemia, vascular calcification, endothelial dysfunction, oxidative stress and hypervolemia accelerate the development of CV in these patients[2)].

Obesity has long been linked to the development of cardiovascular disease, especially to deaths from coronary artery disease, and increasing numbers of studies have confirmed the importance of the relationship[3, 4)]. Obesity is associated with an increase in the

Address for correspondence: Ismail Kocyigit, Erciyes University Medical Faculty, Department of Nephrology, 38039 Kayseri, Turkey
E-mail: iikocyigit@gmail.com
Received: November 19, 2013
Accepted for publication: April 9, 2014

visceral and epicardial adipose tissue (EAT) volume. EAT is visceral adipose tissue which is located subepicardially around the heart. Although little is known about the physiological and metabolic roles of EAT, it has been implicated as a CV risk factor in non-uremic and uremic patients[5, 6]. Recently, Turkmen *et al*. reported higher EAT in dialysis patients compared to healthy controls, and a significant association of EAT with malnutrition-inflammation-atherosclerosis-calcification (MIAC) syndrome[7]. Additionally, it was shown that EAT was correlated with atherosclerosis, arterial stiffness and the presence of coronary calcification in long-term hemodialysis (HD) patients[8].

Thyroid hormone abnormalities are common in ESRD patients[9]. Recent advances in our understanding of the thyroid system have strongly implicated both subclinical hypothyroidism and low free triiodothyronine (fT3) levels in the cardiac and atherosclerotic abnormalities observed in non-renal patients[10]. On the other hand, Tatar *et al*. recently demonstrated that low fT3 levels are associated with carotid atherosclerosis in HD patients[11, 12]. Yilmaz *et al*. demonstrated a relationship between low fT3 levels and endothelial dysfunction in patients suffering from renal failure[13]. Moreover, there is a well-accepted association between low fT3 levels and mortality in patients suffering from renal failure[14]. EAT and low free T3 levels are separate risk factors for CV diseases in patients suffering from renal failure, and Moon *et al*. showed that low levels of fT3 and fT4 were significantly associated with an increased pericardial fat volume in patients without chronic renal failure[15]. However, to the best of our knowledge, the association between EAT and low fT3 levels is unclear.

The aim of this study was to investigate the relationships among the fT3 level, endothelial dysfunction and EAT in PD patients.

Methods

Study Population

This single-center, cross-sectional study was performed on monitored patients undergoing PD at the Nephrology Department of the Medical Faculty of Erciyes University, Turkey, for a period of six months between March 2013 and September 2013. 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 center, the majority (~90%) of dialysis patients are on PD. One hundred and ninety-four PD patients are currently being followed. The patients included in this study were selected from this group on the basis of the following inclusion and exclusion criteria: The inclusion criteria in our study were echocardiogram, FMD and EAT data measured within a period of six months and a blood sample obtained for measurement of the thyroid and gonadal hormones within the same interval. The exclusion criteria were abnormal TSH levels, the use of anti-thyroid medications and cardiovascular issues. In total, 43 patients were excluded because of (I) abnormal TSH levels and/or the use of anti-thyroid medications ($n=17$), (II) the presence of cardiac arrhythmia (atrial fibrillation, a history of supraventricular and ventricular tachycardia attack, cardiac dysrhythmia related to pacemaker use) ($n=6$) and (III) major cardiovascular diseases (history of coronary artery bypass surgery, cardiomyopathy, history of acute coronary syndrome in last six months) as assessed by the medical history and transthoracic echocardiography ($n=20$). In addition, 26 patients who were eligible for the study protocol refused to participate in the study and did not provide informed consent. Finally, this study was conducted in the remaining 125 patients. Twenty-eight percent of the enrolled patients were diabetic. In the study population, 40% and 18% of the patients were receiving treatment with anti-hypertensive agents and statins, respectively. The peritoneal dialysis patients were dialyzed using the Baxter Twin Bag (Baxter Healthcare SA, Castlebar, County Mayo, Ireland) and Fresenius A.N.D.Y Plus or Stay-safe systems (Fresenius Medical Care GmbH, Hamburg, Germany).

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 hours of fasting. The glucose, creatinine and lipid profiles were determined using standard methods. The C-reactive protein (CRP) level was measured using a BN2 model nephelometer (Dade-Behring, Germany). Tri-potassium EDTA based anticoagulated blood samples were drawn to determine the complete blood cells counts (Sysmex K-1000 auto analyzer, Block Scientific, USA) within 30 min of sampling.

The serum prolactin levels were quantified using the Siemens Advia Centaur XP Immunoassay System. Prolactin was measured with an Advia Centaur PRL Immunoassay Kit from Bayswater (Victoria, Australia). The lower limit of detection for prolactin was 3.3 ng/mL. The serum total testosterone levels were quantified by a Immulite 2000 XP Immunoassay System using an Immulite 2000/System 2000 TES Kit from Lianberis (Gwynedd, U.K.). The lower limit of detec-

tion for total testosterone was 0 ng/mL. The serum progesterone and estradiol (E2) levels were quantified by a Siemens Advia Centaur XP Immunoassay System. Progesterone was measured with an Advia Centaur PRGE Immunoassay Kit from Bayswater (Victoria, Australia). The lower limit of detection for progesterone was 0.21 ng/mL. E2 was measured with an Advia Centaur CP E2 Immunoassay Kit from Bayswater (Victoria, Australia). The lower limit of detection for E2 was 18.9 ng/mL.

The serum TSH, free T_4 (fT_4) and free T_3 (fT_3) levels were quantified by the Siemens Advia Centaur XP Immunoassay System using the Advia Centaur FT3-FT4-TSH3UL Kit from Bayswater (Victoria, Australia). The reference values were: 0.57-5.6 mIU/L for TSH, 0.88-1.72 ng/dL for fT_4 and 3.54-6.82 pg/mL for fT_3.

Echocardiography and Epicardial Adipose Tissue Measurement

All participants underwent transthoracic echocardiography imaging 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 EAT 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 EAT was performed two weeks later in order to assess the inter-observer and intra-observer variability. Echocardiographic assessments of the EAT were performed according to the method described previously by Iacobellis *et al.*[16]. The epicardial fat was identified as an echo-free space in the pericardial layer by two-dimensional echocardiography[17, 18]. The maximum EAT 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 anatomical landmark at end-diastole in three cardiac cycles. The inter-observer and intra-observer variabilities of the EAT were found to be 3.5% and 2.9%, respectively.

Endothelial Function Test

Endothelial dysfunction was assessed according to the method described by Celermajer *et al.*[19]. Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA, USA) with a 12- Mhz probe. The subjects remained at rest in the supine position for at least 15 min before the examination started. Each subject's right arm was comfortably immobilized in the extended position to allow for consistent recording of the brachial artery 2-4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single 2D frames. All ultrasound images were recorded on a Super Video Home System (SVHS) videotape for the subsequent blinded analysis. The maximum flow-mediated vasodilation (FMD) diameters were calculated as the average of the three consecutive maximum diameter measurements after hyperemia and nitroglycerin, respectively. The FMD was then calculated as the percentage change in the diameter compared with the baseline resting diameters.

Ambulatory Blood Pressure Measurements

24-hour blood pressure monitoring was performed using a Del Mar Medical Ressurometer Model P6 (Del Mar Reynolds, Irvine, CA, USA), and the results were assessed using the manufacturer's computer software program. Ambulatory measurements were conducted once every 15 minutes from 7 AM until 11 PM, and then once every 30 minutes from 11 PM until 7 AM.

The evaluation was performed by taking the mean values of the day and night blood pressures into account. Hypertension was considered to be present if the average systolic pressure was ≥ 130 mm Hg and/or the average diastolic pressure was ≥ 80 mmHg for the whole day, or if the individual was taking antihypertensive medication.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov- Smirnov test. For continuous variables, the results are presented as the mean values ± SD for parametric variables (normal data distribution) or as medians (minimum, maximum) for non-parametric variables (those without a normal data distribution). The differences between the two groups were evaluated with Student's *t*-test (normal distribution) or the Mann- Whitney *U*-test (those without a normal distribution). Pearson correlation coefficients were calculated to examine the degree of association between the variables. A p value < 0.05 was considered to be significant. Variables for which the unadjusted univariate p value was < 0.10 in the linear regression analysis were included in the multivariate analysis. Variables were considered to be significant at $p < 0.10$ in the univariate analysis, and were included in the

Table 1. The demographics, hormonal and biochemical data of the patients with PD categorized according to the serum fT_3 levels

Parameters	Overall ($n=125$)	fT_3		p
		Low T3 $n=35$	Normal T3 $n=90$	
Age (years)	51 ± 13	54.7 ± 11.5	50.7 ± 13.8	0.124
Gender (F/M)	49/76	16/19	33/57	0.233
Duration of dialysis	36 (3, 184)	39.0 (2.0-184.0)	35.5 (1.0-169.0)	0.529¥
Presence of diabetes mellitus	35	8	27	0.90
Use of anti-hypertensive agents	50	14	36	0.80
Use of statins	22	5	17	0.90
BMI (kg/m^2)	28.4 ± 4.82	29.5 ± 5.05	27.2 ± 4.4	**0.035**
D/P creatinine	0.72 ± 0.91	0.73 ± 0.17	0.71 ± 0.48	0.602
Kt/V	2.44 ± 0.59	2.35 ± 0.66	2.53 ± 0.58	0.311
Platelet count (×1,000/mm^3)	254 ± 78	274.0 ± 99.9	247 ± 67.7	0.151
Hemoglobin (g/L)	11.2 ± 1.7	10.9 ± 1.72	11.4 ± 1.78	0.215
White blood cell count (10^3/uL)	7.3 ± 2.1	8.11 ± 2.28	7.04 ± 2.00	0.011
Creatinine (mg/dL)	8.3 ± 3.7	8.83 ± 3.30	8.13 ± 3.88	0.351
Plasma fasting glucose (mg/dL)	103 (72, 358)	112.0 (81.0-279.0)	98.0 (72.0-358.0)	**0.041**¥
Phosphorus (mg/dL)	4.3 ± 1.2	4.47 ± 1.16	4.33 ± 1.21	0.548
Calcium (mg/dL)	9.4 ± 0.9	9.57 ± 1.16	9.39 ± 0.88	0.340
Fasting total cholesterol (mg/dL)	196 ± 52	205.02 ± 68.07	192.54 ± 45.32	0.236
Fasting LDL cholesterol (mg/dL)	118 ± 42	124.17 ± 53.05	113.58 ± 37.01	**0.047**
Fasting triglycerides (mg/dL)	157 (50, 670)	159.0 (58.0-480.0)	155.0 (50.0-670.0)	0.884¥
Serum albumin (g/dL)	3 (1.6, 3.9)	2.70 (1.60-3.70)	3.10 (1.90-3.90)	**<0.001**¥
fT_4 (pg/mL)	1.1 ± 0.1	1.04 ± 0.19	1.14 ± 0.19	0.010
TSH (μU/mL)	2.6 (0.03, 68.5)	4.79 (1.20-68.5)	2.03 (0.03-8.09)	**<0.001**¥
Prolactin	14.8 (1.9, 273)	16.2 (1.90-198.79)	14.5 (5.74-273.14)	0.402¥
Progesterone (only in females)	0.63 (0.04, 5.6)	0.55 (0.07-2.45)	0.67 (0.04-5.60)	0.787¥
Estradiol (only in females)	15.2 (11.2, 319)	14.04 (11.6-96.86)	16.58 (11.20-319.11)	0.233¥
Testosterone (only in males)	419 ± 86	360.47 ± 122.40	440.11 ± 209.53	0.050
Hs-CRP (mg/L)	17 (3.4, 84)	17.0 (4.20-84.0)	12.0 (3.40-54.0)	**0.038**¥
FMD (%)	8.4 ± 1.9	7.44 ± 1.98	8.90 ± 1.75	**<0.001**
EFT (mm)	6.7 ± 2.9	8.43 ± 3.26	6.08 ± 2.49	**0.001**
Office (mmHg)				
Systolic BP	124 ± 10	126.02 ± 10.61	123.51 ± 10.51	0.053
Diastolic BP	88 ± 6	89.62 ± 6.97	87.70 ± 6.25	0.137
Mean BP	100 ± 6	102.42 ± 6.43	99.63 ± 5.53	**0.017**
ABPM (mmHg)				
Systolic BP	125 ± 9	128.14 ± 9.72	124.64 ± 9.61	0.071
Diastolic BP	87 ± 5	89.71 ± 6.10	86.61 ± 5.06	**0.004**
Mean BP	100 ± 5	102.52 ± 5.84	99.28 ± 4.87	**0.002**

BP, blood pressure; hs-CRP, high sensitivity C-reactive protein; BMI, body mass index; LDL, low-density lipoprotein; FMD, flow mediated dilatation; EFT, epicardial fat thickness; ABPM, ambulatory blood pressure measurement

The values are the means ± SD or medians (minimum-maximum), as appropriate. Bold values indicate significant differences between the uric acid groups ($p<0.05$).

*p = chi square value

¥p = non-parametric analysis

model. We reduced the model by using backwards elimination at a $p<0.10$ stringency level in the multivariate linear regression analysis. A p value <0.05 was considered to be significant, and the confidence interval (CI) was set at 95%. All statistical analyses were performed using the SPSS version 15 software pro-

Table 2. The univariate correlates for epicardial adipose tissue and fT_3 in all 125 study participants

Parameters	EFT (mm)		fT_3 (pg/mL)	
	r	*p*	*r*	*p*
EAT (mm)	–	–	−0.29	**0.001**
fT_3 (pg/mL)	−0.29	**0.001**	–	–
Age (years)	0.20	**0.04**	−0.23	**0.008**
Duration of dialysis	−0.10	0.24	−0.20	**0.02**
FMD (%)	−0.36	**<0.001**	0.34	**<0.001**
hs-CRP (mg/L)	0.30	**0.001**	−0.26	**0.003**
Serum albumin level (g/dL)	−0.13	0.20	0.32	**<0.001**
Plasma triglycerides (mg/dL)	−0.01	0.84	0.01	0.91
HDL cholesterol (mg/dL)	0.09	0.92	0.10	0.26
Total cholesterol (mg/dL)	0.10	0.28	−0.16	0.08
BMI (kg/m^2)	0.23	**0.02**	−0.21	**0.03**
Office (mmHg)				
Systolic BP	0.26	**0.004**	−0.16	0.06
Diastolic BP	0.07	0.45	−0.16	0.06
Mean BP	0.22	**0.01**	−0.20	**0.01**
ABPM (mmHg)				
Systolic BP	0.25	**0.006**	−0.18	**0.03**
Diastolic BP	0.14	0.12	−0.33	**<0.001**
Mean BP	0.24	**0.008**	−0.30	**0.001**

hs-CRP, high sensitivity C-reactive protein; LDL, low-density-lipoprotein; FMD, flow mediated dilatation; EFT, epicardial fat thickness; BMI, body mass index; ABPM, ambulatory blood pressure measurement
Bold values are significant ($p<0.05$).

gram (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the Patients with High or Low Serum fT3 Levels

The demographic, clinical and laboratory characteristics of the study population are shown in **Table 1**. Patients were divided according to the serum fT_3 values (within the normal range and below the reference level). Compared with the patients in the low fT_3 group, those in the normal fT3 group had higher serum albumin levels ($p<0.001$), FMD (<0.001) and a lower BMI ($p=0.035$), lower plasma fasting glucose level ($p=0.041$), EFT ($p=0.001$), TSH ($p<$ 0,001), hs-CRP ($p=0.038$), LDL cholesterol ($p=$ 0.047), mean BP in the office measurements ($p=$ 0.017) and both the diastolic BP ($p=0.004$) and mean BP ($p=0.002$) in the ABPM measurements. All other parameters were similar between the groups.

Univariate Correlations with the EFT

The univariate correlations with EFT are shown in **Table 2**. In the whole cohort, EFT correlated with the fT3, age, FMD, hs-CRP level, BMI, systolic BP and mean BP levels, but not with the duration of dialysis, cholesterol, diastolic BP, triglycerides or albumin level. Meanwhile, the fT_3 correlated with EFT, age, duration of dialysis, FMD, hs-CRP level, albumin level, BMI and the blood pressure measured by ABPM and the mean BP of office measurements, but not with the cholesterol levels, triglycerides or systolic and diastolic BP of the office measurements. EAT inversely correlated with the FMD ($r=-0.37$, $p<0.001$) and fT_3 level ($r=-0.26$, $p=0.004$; (**Fig. 1**)

Multivariate Regression Analysis

As shown in **Table 3**, we constructed a multivariate regression analysis model to assess the relative independence of the observed correlations. The model was adjusted for age, the hs-CRP level, mean ABPM, BMI and fT_3 level. We used a multivariate linear regression analysis with backward elimination, and compared the retained predictors using likelihood ratio tests. EFT was predicted by the hs-CRP level ($\beta=$ 0.17, $p=0.03$) and fT_3 level ($\beta=-0.25$, $p=0.02$).

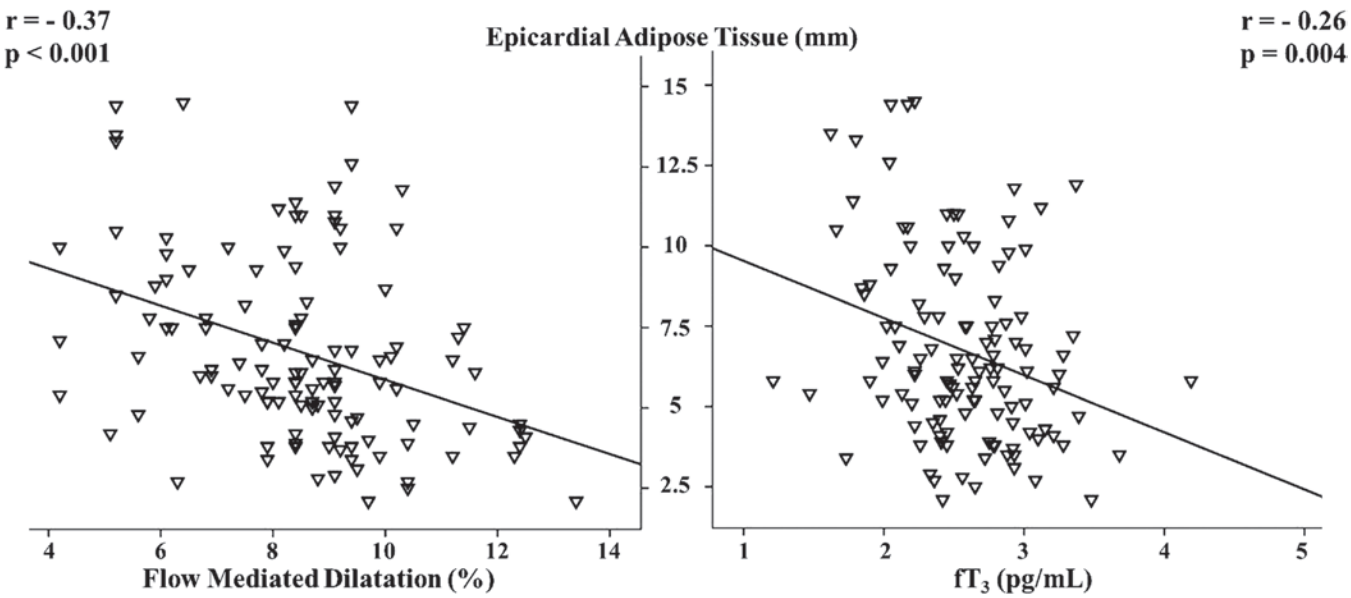

Fig. 1. The univariate correlations of EFT with the FMD and the fT_3 level in the study population.

Table 3. The results of the multiple regression model using the factors associated with the dependent variable in the univariate analysis to predict EFT in all study subjects ($n = 125$)

Variables	EFT (mm) (model adj $r^2 = 0.31$)		*p*
	B	Std. errors	
Age, years	0.18	0.01	0.06
hs-CRP, mg/L	0.17	0.01	**0.03**
Mean ABPM, mmHg	0.17	0.02	0.07
fT3, pg/mL	−0.25	0.12	**0.02**

The original models included the age, hs-CRP, fT3, BMI and mean BP (ambulatory).
hs-CRP, high sensitivity C-reactive protein; ABPM, ambulatory blood pressure measurement; EFT, epicardial fat thickness
Adjusted $r^2 = 0.31$ for the EAT
Bold values are significant

Discussion

Epicardial adipose tissue is associated with cardiovascular events in ESRD patients. Although the association between low fT3 levels and EAT in patients without renal failure has been well established, the relationship between low fT3 levels and EAT in peritoneal dialysis patients has been unclear. In addition, tEAT has recently been shown to be a predictor of mortality in hemodialysis patients[20]. To the best of our knowledge, ours is the first study to investigate the association between the fT3 levels and EAT in a population of patients being treated with peritoneal dialysis. Our findings suggest that the fT3 level is associated with EAT in the PD population, and could be a predictive factor for the cardiovascular outcomes.

Epicardial adipose tissue is a visceral adipose fat depot that is located subepicardially around both ventricles of the heart, with variable extent and distribution patterns[21]. EAT is metabolically active and acts as a secretory tissue. Several bioactive inflammatory adipokines and cytokines, such as adiponectin, TNF-alpha, IL-1, IL-6 and resistin are released from EAT[22]. These molecules have been proposed to be responsible for the cardiac effects of EAT[23]. Epicardial adipose tissue can be calculated using several methods, including computed tomography (CT), magnetic resonance

imaging (MRI) or echocardiography. Direct measurement of the epicardial adipose tissue thickness via echocardiography is another reliable method that can be used to measure the visceral adiposity[24].

Recent interest has shifted towards the association between the EAT and cardiovascular diseases. An increased amount of EAT. as demonstrated by echocardiographic measurements, is associated with carotid atherosclerosis and the arterial stiffness in different populations, such as patients with diabetes mellitus and hypertension[25, 26]. Only a few studies have so far been conducted in patients with renal disease on this issue. Turkmen *et al.* revealed that the volume of EAT increased in patients with ESRD, and EAT was related to the age, body mass index and malnutrition inflammation atherosclerosis (MIA) syndrome components[7]. In support of this, we also observed that EAT was related to the age, BMI and CRP levels. Turan *et al.* showed that an increased EAT volume in patients who were treated with hemodialysis for a long time was associated with carotid atherosclerosis, arterial stiffness and coronary calcification. They suggested that the measurement of EAT in these patients can be used as a predictor of vascular injury[8].

Endothelial dysfunction is an independent predictor of cardiovascular disease. In the literature, some studies have been conducted on the relationships between EAT and endothelial dysfunction in patients with or without renal disease. Sade *et al.* demonstrated a negative association between EAT and the coronary flow reserve in patients with angiographically normal coronary arteries[27]. Atakan *et al.* also demonstrated a negative association between the EAT and the coronary flow reserve in 71 patients on chronic hemodialysis[28]. FMD measurement is also a predictor of endothelial dysfunction. In agreement with these previous studies, we also observed a strong, significant, negative association between EAT and FMD in our study, which supports the idea that EAT may be related to endothelial dysfunction.

Several studies have investigated the relationship between EAT and arterial blood pressure, as well as endothelial dysfunction. A strong association between hypertension and an increased amount of EAT has been shown in both echocardiographic and autopsy results[29, 30]. Consistent with the current literature, we also observed a significant relationship among the office arterial blood pressure, ambulatory arterial blood pressure and EAT. Both the office and ambulatory blood pressure monitoring measurements showed that the systolic blood pressure was positively correlated with EAT.

Several changes may be seen in the metabolism of thyroid hormones in ESRD patients. Some changes have been reported in the hypothalamus-hypophysis-thyroid axis and peripheral thyroid hormone metabolism, and dysfunctional thyroid hormone metabolism becomes more prevalent with the progression of chronic kidney disease, ranging from 5% to 25% as the stage of kidney disease worsens[31]. The prevalence of low fT3 levels in ESRD patients was reported to be approximately 20-25%[31]. Consistent with the literature, this ratio was found to be 25% in our study. Tatar *et al.* revealed that low fT3 levels are associated with increased carotid atherosclerosis and arterial stiffness[11]. T3 is a potent stimulus for NO-dependent vasodilatation in the forearm in healthy subjects. It has also been shown that there is an association between low fT3 levels and endothelial dysfunction in stage 3-4 chronic kidney disease patients[13]. We also observed a significant relationship between the fT3 levels and FMD in our study; which supports that fT3 affects the endothelial function. Hypertension, hyperlipidemia, hypercoagulability, hyperhomocysteinemia and inflammation could all be responsible for the endothelial dysfunction in patients with thyroid dysfunction[12]. Moreover, a low fT3 level has been shown to be associated with inflammation and cardiovascular disease[32]. Carrero *et al.* reported that low fT3 levels were inversely correlated with markers of inflammation, including IL-6 and CRP[33]. Recently, Zoccali *et al.* suggested that low fT3 levels may be considered as an independent predictor of mortality in ESRD patients[34]. On the other hand, Ozen *et al.* showed that the serum fT3 level is a strong and inverse mortality predictor, which is partly explained by its underlying association with malnutrition and inflammation[14]. We also observed a significantly negative association between low fT3 levels and the CRP levels in our study.

There is some evidence that epicardial fat tissue is an active endocrine organ. Studies have revealed that EAT is a source of several proinflammatory and proatherogenic cytokines[21-23]. We also found a significant association between an inflammatory marker, hs-CRP, and EAT. Inflammation, which is common in ESRD patients, may be the reason for the increased hs-CRP levels. Moreover, it is not clear whether EAT or ESRD is the origin of the inflammation, or whether both make contributions. Further studies are needed to clarify the potential mechanism(s) underlying the development of inflammation.

The relationship between a low fT3 level and EAT remains unclear. Moon *et al.* found a significant association between low fT3 levels and increased pericardial tissue in a population which consisted of 100

euthyroid male patients[15]. However, no previous studies have examined this issue in patients with PD. Ours is the first study to do so. Low free T3 levels were found to be related to an increased amount of EAT, and the free T3 level was found to be a predictor of EAT according to the results of a multivariate analysis in our study. Moon *et al.*[15] also found an inverse relationship between the free T3 levels and BMI in their study, and similar results were observed in our study.

There are some limitations associated with our study. First, it is a cross-sectional study. Second, the epicardial adipose tissue thickness was measured via echocardiography instead of computed tomography or MRI. However, echocardiography has several advantages in comparison with CT and MRI, such as the fact that it is more easily accessible, has a low cost and does not require X-ray exposure. EAT obtained by CT or MRI may be more accurate than that obtained by echocardiography, because both CT and MRI use volumetric values, while echocardiography could provide only information about the thickness of EAT. Third, the levels of hormones were studied only one time.

In conclusion, thyroid dysfunction and low fT3 levels are common among patients treated with peritoneal dialysis. Low fT3 levels are associated with the epicardial adipose thickness. Further studies are needed to evaluate the pathogenesis in association with these findings and to support the present findings.

Funding

No funding has been received for this study.

Conflict of Interest

The authors declare no conflicts of interest.

References

1) Sipahioglu MH, Kucuk H, Unal A, Kaya MG, Oguz F, Tokgoz B, Oymak O, Utas C: Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients. Perit Dial Int, 2012; 32: 73-80
2) García de Vinuesa S, Gómez-Campderá F, Goicoechea MA, Luño J: Risk of cardiovascular disease associated to chronic renal disease. Prevalence and control degree of classical risk factors. Nefrologia, 2005; 25: 18-22
3) Cronin O, Morris DR, Walker PJ, Golledge J: The association of obesity with cardiovascular events in patients with peripheral artery disease. Atherosclerosis, 2013; 228: 316-323
4) Cronin O, Walker PJ, Golledge: The association of obesity with abdominal aortic aneurysm presence and growth. Atherosclerosis, 2013; 226: 321-327
5) Lee HY, Després JP, Koh KK: Perivascular adipose tissue in the pathogenesis of cardiovascular disease. Atherosclerosis, 2013; 230: 177-184
6) D'Marco LG, Bellasi A, Kim S, Chen Z, Block GA, Raggi P: Epicardial adipose tissue predicts mortality in incident hemodialysis patients: a substudy of the Renagel in New Dialysis trial. Nephrol Dial Transplant, 2013; 28: 2586-2595
7) Turkmen K, Kayikcioglu H, Ozbek O, Solak Y, Kayrak M, Samur C, Anil M, Zeki Tonbul H: The relationship between epicardial adipose tissue and malnutrition, inflammation, atherosclerosis/calcification syndrome in ESRD patients. Clin J Am Soc Nephrol, 2011; 6: 1920-1925
8) Turan MN, Gungor O, Asci G, Kircelli F, Acar T, Yaprak M, Ceylan N, Demirci MS, Bayraktaroglu S, Toz H, Ozkahya M, Ok E: Epicardial adipose tissue volume and cardiovascular disease in hemodialysis patients. Atherosclerosis, 2013; 226: 129-133
9) Iglesias P, Díez JJ: Thyroid dysfunction and kidney disease. Eur J Endocrinol, 2009; 160: 503-515
10) Danzi S, Klein I: Thyroid hormone and the cardiovascular system. Med Clin North Am, 2012; 96: 257-268
11) Tatar E, Kircelli F, Asci G, Carrero JJ, Gungor O, Demirci MS, Ozbek SS, Ceylan N, Ozkahya M, Toz H, Ok E: Associations of triiodothyronine levels with carotid atherosclerosis and arterial stiffness in hemodialysis patients. Clin J Am Soc Nephrol, 2011; 6: 2240-2246
12) Tatar E, Kircelli F, Ok E: The contribution of thyroid dysfunction on cardiovascular disease in patients with chronic kidney disease. Atherosclerosis, 2013; 227: 26-31
13) Yilmaz MI, Sonmez A, Karaman M, Ay SA, Saglam M, Yaman H, Kilic S, Eyileten T, Caglar K, Oguz Y, Vural A, Yenicesu M, Zoccali C: Low triiodothyronine alters flow-mediated vasodilatation in advanced nondiabetic kidney disease. Am J Nephrol, 2011; 33: 25-32
14) Ozen KP, Asci G, Gungor O, Carrero JJ, Kircelli F, Tatar E, Sevinc Ok E, Ozkahya M, Toz H, Cirit M, Basci A, Ok E: Nutritional state alters the association between free triiodothyronine levels and mortality in hemodialysis patients. Am J Nephrol, 2011; 33: 305-312
15) Moon MK, Hong ES, Lim JA, Cho SW, Soo L, Choi SH, Yi KH, Park do J, Park YJ, Jang HC: Associations between thyroid hormone levels and regional fat accumulation in euthyroid men. Eur J Endocrinol, 2013¸29; 168: 805-810
16) Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, Leonetti F: Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res, 2003; 11: 304-310
17) Silaghi AC, Poant L, Valea A, Pais R, Silaghi H: Is epicardial adipose tissue, assessed by echocardiography, a reliable method for visceral adipose tissue prediction? Med Ultrason, 2011; 13: 15-20
18) Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F: Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: A

new indicator of cardiovascular risk. J Clin Endocrinol Metab, 2003; 88: 5163-5168
19) Celermajer DS, Sorensen K, Ryalls M, Robinson J, Thomas O, Leonard JV, Deanfield JE: Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. J Am Coll Cardiol, 1993; 22: 854-858
20) D'Marco LG, Bellasi A, Kim S, Chen Z, Block GA, Raggi P: Epicardial adipose tissue predicts mortality in incident hemodialysis patients: a substudy of the Renagel in New Dialysis trial. Nephrol Dial Transplant, 2013; 28: 2586-2595
21) Iacobellis G, Bianco AC: Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab, 2011; 22: 450-457
22) Ouwens DM, Sell H, Greulich S, Eckel J: The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease. J Cell Mol Med, 2010; 14: 2223-2234
23) Sacks HS, Fain JN: Human epicardial adipose tissue: a review. Am Heart J, 2007; 153: 907-917
24) Iacobellis G, Willens HJ: Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr, 2009; 22: 1311-1319
25) Natale F, Tedesco MA, Mocerino R, de Simone V, Di Marco GM, Aronne L, Credendino M: 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, 2009; 10: 549-555
26) Sengul C, Cevik C, Ozveren O, Oduncu V, Sunbul A, Akgun T, Can MM, Semiz E, Dindar I: Echocardiographic epicardial fat thickness is associated with carotid intima-media thickness in patients with metabolic syndrome. Echocardiography, 2011; 28: 853-858
27) Sade LE, Eroglu S, Bozbaş H, Ozbiçer S, Hayran M, Haberal A, Müderrisoğlu H: Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. Atherosclerosis, 2009; 204: 580-585
28) Atakan A, Macunluoglu B, Kaya Y, Ari E, Demir H, Asicioglu E, Kaspar C: Epicardial fat thickness is associated with impaired coronary flow reserve in hemodialysis patients. Hemodial Int, 2013 Sep 4
29) Ertas F, Kaya H, Acet H, Cil H, Akyüz A, Islamoğlu Y, Tekbaş E, Aritürk Z, Aydin M, Soydinç S: Increased echocardiographic epicardial fat thickness is related to impaired diurnal blood pressure profiles. Blood Press, 2012; 21: 202-208
30) Dicker D, Atar E, Kornowski R, Bachar GN: Increased Epicardial Adipose Tissue Thickness as a Predictor for Hypertension: A Cross-Sectional Observational Study. J Clin Hypertens (Greenwich), 2013 Sep 19
31) Lim VS: Thyroid function in patients with chronic renal failure. Am J Kidney Dis, 2001; 38: 80-84
32) Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F: Low triiodothyronine: a new facet of inflammation in end-stage renal disease. J Am Soc Nephrol, 2005; 16: 2789-2795
33) Carrero JJ, Qureshi AR, Axelsson J, Yilmaz MI, Rehnmark S, Witt MR, Bárány P, Heimbürger O, Suliman ME, Alvestrand A, Lindholm B, Stenvinkel P: Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. J Intern Med, 2007; 262: 690-701
34) Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P: Low triiodothyronine and survival in end-stage renal disease. Kidney Int, 2006; 70: 523-528