

EPICARDIAL FAT THICKNESS IN HEMODIALYSIS PATIENTS

Original Article

HEMODİYALİZ HASTALARINDA EPİKARDİYAL YAĞ DOKUSU KALINLIĞI

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ABSTRACT

Background: Cardiovascular disease (CVD) is the main cause of mortality in hemodialysis (HD) patients. Epicardial fat tissue (EFT) is a new risk factor in CVD. The aim of this study was to determine EFT thickness in HD patients.

Methods and results: We performed a cross-sectional study including 71 chronic HD patients and 65 age and sex-matched healthy controls. EFT was measured by using transthoracic Doppler echocardiography. EFT was found to be significantly higher in HD patients when compared to healthy controls (6.53 ± 1.01 mm vs. 5.79 ± 1.06 mm respectively, $p < 0.001$).

Conclusion: This study demonstrated that EFT was significantly higher among HD patients compared to healthy controls. EFT thickness measured by TTDE could be a useful marker for CVD risk assessment in HD patients.

Key words: Epicardial fat tissue; hemodialysis; cardiovascular disease.

ÖZET

Giriş ve Amaç: Hemodiyaliz hastalarında kardiyovasküler hastalıklar mortalitenin en önemli nedenidir. Son yıllarda kardiyovasküler hastalık gelişiminde etkili yeni risk faktörü olarak epikardiyal yağ dokusu tanımlanmıştır. Çalışmamızda kardiyovasküler hastalık gelişim riski yüksek olan hemodiyaliz hastalarında epikardiyal yağ dokusunun kalınlığının ölçümü hedeflenmiştir.

Metod ve sonuçlar: Çalışmamıza 71 kronik hemodiyaliz hastası ve cinsiyet ile yaş eşleştirilmiş 65 sağlıklı kontrol dahil edilmiştir. Epikardiyal yağ dokusu, transtorasik Doppler ekokardiyografi (TTDE) ile değerlendirilmiştir. Sonuçta hemodiyaliz hasta grubunda epikardiyal yağ dokusu kalınlığının kontrol grubuna göre anlamlı olarak artmış olduğu

saptanmıştır (6.53 ± 1.01 mm vs. 5.79 ± 1.06 mm respectively, p<0.001).

Özet: Çalışmamızda hemodiyaliz hastalarında epikardiyal yağ dokusu kalınlığının anlamlı olarak arttığı saptanmıştır. Hemodiyaliz hastalarında TTDE ile epikardiyal yağ dokusu kalınlığının ölçümü, bu hasta grubunda kardiyovasküler risk tayininde anlamlı olabilir.

Anahtar kelimeler: Epikardiyal yağ dokusu; hemodiyaliz; kardiyovasküler hastalık.

INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is the most common cause of mortality in hemodialysis (HD) patients (1,2). In addition to classical risk factors, left ventricular hypertrophy, coronary artery calcification, hyperparathyroidism, chronic inflammation and endothelial dysfunction (ED) have all been associated with CVD in HD patients (3-5).

Epicardial fat tissue (EFT) is the visceral adipose tissue surrounding the subepicardial coronary vessels which covers 80% of the cardiac surfaces and accounts for 20% of the total heart weight. Recently it has been recognized as a new risk factor for atherosclerotic CVD in non-uremic patients (6-9). EFT has the same origin as abdominal visceral fat tissue and secretes proatherosclerotic and proinflammatory cytokines, such as TNF- α , IL-6 and several adipocytokines, which might play a role in atherosclerotic CVD (10-13). Interestingly, the relationship between atherosclerosis and EFT is independent of diabetic status and body mass index (14). Even though the association between EFT and atherosclerosis in the non-uremic population has been shown in a recent meta-analysis (15), the role of EFT in HD patients still remains unknown. In a recent study, Turan et al reported that EFT was associated with carotid intima thickness, arterial stiffness and coronary

artery calcification; however this association lost its significance after adjusting for other atherosclerotic risk factors (16). On the other hand, Turkmen et al. showed an association between EFT volume and coronary artery calcification in peritoneal dialysis patients (17). Recent studies evaluated the association between EFT and atherosclerosis in dialysis patients by measuring carotid intima thickness, arterial stiffness and coronary artery calcification (16,17).

The aim of this study was to investigate the EFT thickness in hemodialysis patients.

MATERIAL-METHOD

Seventy-one non-diabetic HD patients (25 male, 46 female) and 65 (23 male, 42 female) age and sex-matched healthy controls were included in the study. All HD patients had creatinine clearances of less than 10 ml/min/1.73 m² and had been on chronic HD programme thrice weekly with 4-hour sessions with bicarbonate containing dialysate for at least one year. The blood flow rate was kept between 300-350 ml/min whereas the dialysate flow rate was kept at 500 ml/min. Kt/V was equal to or more than 1.4. All of the patients were maintained at their target dry body weight. Healthy individuals without any chronic disease were included as the control group. None of the healthy individuals were taking antibiotics, corticosteroids, cytotoxic drugs, vitamin supplementations or any kind of medications. Both the patient and control groups were non-smokers and did not consume alcohol. Exclusion criteria were defined as preexisting valvular heart disease, myocardial infarction, any prior coronary intervention, dilated or hypertrophic cardiomyopathy, congestive heart failure and cardiac arrhythmia. Individuals in whom the left anterior descending artery was not visualized adequately by Doppler echocardiography were also excluded. Eighteen patients were on treatment with antihypertensive drugs with 7, 3 and 8 patients receiving

angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) and beta blocker therapy, respectively. Thirty-two patients were on calcium-containing phosphate binder therapy and 28 patients were taking vitamin D. None of the patients received statine therapy. All study patients and healthy controls gave written informed consent. The study has been approved by the local ethics committee and has therefore been performed in accordance with the ethical standards of the Helsinki declaration.

SAMPLE COLLECTION AND ANALYSIS

Fasting serum samples were obtained in the early morning for biochemical studies. All biochemical blood samples were measured prior to the midweek HD session. Blood samples were drawn from all patients (before HD session) and controls into vacutainer tubes containing lithium heparin as anticoagulant. After centrifugation (+4°C, 5000 rpm, 10 min.), the plasma was harvested and stored at -80°C until biochemical analyses.

EFT MEASUREMENT

Each patient underwent transthoracic echocardiography performed with a VIVID 7 (GE, USA) instrument according to standard techniques in the left lateral decubitus position. Echocardiographic images were recorded onto a computerized database and videotape. EFT was measured on the free wall of right ventricle from the parasternal long-axis view. EFT was defined as an echo-free space between pericardial layers on the 2-dimensional echocardiography. EFT was measured perpendicularly on the free wall of right ventricle at end-diastole for 3 cardiac cycles. In order to standardize the measuring point between different observers, we used the aortic annulus as an anatomical reference. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam

perpendicular to the aortic annulus. The average value measured from 3 cardiac cycles for each echocardiographic view was used for the statistical analysis.

STATISTICS

Descriptive statistics for continuous variables were expressed as mean \pm standard deviation (SD). Two independent samples t-test was used to compare means of control and patient groups for EFT and CFR levels. Pearson's correlation test was performed to explore the linear relationships between EFT and CFR levels. A multiple regression analysis was used to determine the independent predictors of EFT. Age, BMI, mean arterial pressure, total cholesterol, triglyceride, LDL cholesterol levels and CFR were incorporated in to the model as independent variables. A p-value <0.05 was interpreted as statistically significant. All statistical analysis was performed with statistical analysis programme (SPSS 13.0 for Windows).

RESULTS

Patient characteristics and clinical findings.

The baseline characteristics of the 71 patients (mean age 45 ± 14 years) and 65 controls (mean age 44 ± 8 years) are presented in Table-1. There were no differences regarding age, gender, body mass index (BMI) and systolic/diastolic blood pressure levels between the two groups. Serum cholesterol, triglyceride and glucose levels were also similar in both groups. Serum parathyroid hormone levels were significantly higher in the patient group as expected (305 ± 64.20 vs. 40.88 ± 24.20 pg/ml, $p < 0.05$) (**Table-1**).

	Hemodialysis group (n=71)	Control group (n=65)	p value
Age (years)	45 ± 14	44 ± 8	0.121
Sex (male/female)	25/46	23/42	0.094
BMI (kg/m ²)	24.16 ± 6.48	25.24 ± 6.01	0.106
Dialysis (months)	54 ± 26	0	
SBP (mmHg)	121.45 ± 27.02	120.68 ± 18.50	0.118
DBP (mmHg)	72.15 ± 12.56	68.00 ± 10.04	0.087
MAP (mmHg)	88.58 ± 17.38	85.56 ± 12.86	0.091
Glucose (mg/dL)	92.50 ± 12.35	86.30 ± 13.45	0.085
Total Chol.(mg/dL)	191.35 ± 28.60	184.10 ± 27.48	0.071
LDL Chol.(mg/dL)	114.72 ± 28.44	108.65 ± 26.12	0.093
HDL Chol. (mg/dL)	32.44 ± 11.78	44.55 ± 17.64	0.069
Triglycerides (mg/dL)	152.40 ± 65.22	161.58 ± 48.60	0.062
PTH (pg/mL)	305.40 ± 64.20*	40.88 ± 24.20	0.005
CRP(mg/L)	1.6 ± 1.5	1.5 ± 1.3	0.082

Table 1. Clinical and demographic characteristics of study groups.

Data is presented as mean ± SD. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, LDL: low density lipoprotein, HDL: high density lipoprotein, PTH: parathormone, Chol: Cholesterol, CRP: C- reactive protein , *p<0,05 vs. control

EFT values

EFT was significantly higher in HD patients as compared to healthy controls (6.53 ± 1.01 vs. 5.79 ± 1.06 mm respectively, p<0.001) (Table-2). In the univariate correlation analysis, EFT was positively correlated with age, BMI and total cholesterol levels (**Table 2**).

Parameters	r	p value
Age (years)	0.287	0.001
Total cholesterol (mgr/dl)	0.345	<0.001
BMI	0.380	<0.001

Table 2. Univariate correlation analysis of parameters of HD patients related to EFT thickness

Multiple linear regression analysis was used to define independent determinants of EFT in HD patients. Age, BMI, mean arterial pressure, total cholesterol, triglyceride, LDL cholesterol were all incorporated into the model. According to linear regression analysis, age, BMI, total cholesterol levels and were found to be independent predictors of EFT .

DISCUSSION

This study was designed to assess EFT thickness among HD patients. The main findings of this study were as follows; i) EFT measured by TTDE was significantly higher in HD patients, ii) EFT thickness was positively correlated with age, BMI and total cholesterol levels.

The great burden of CVD and its high mortality rates force investigators to find modifiable new risk factors and define the underlying pathophysiologic mechanisms of atherosclerosis in HD patients. Recently, EFT has been defined as a risk factor for CVD in the non-uremic population (9,15). EFT originates from the splanchnopleuric mesoderm like the abdominal visceral fat deposits and is metabolically an active organ producing several cytokines, including TNF- α , IL-6, omentin, leptin, angiotensinogen and PAI-1, which are mostly proinflammatory and proatherogenic (12,14,23-25). In health, EFT plays a buffering role by scavenging free fatty acids (FFA) that are toxic to the myocardium while under ischemic conditions such as atherosclerosis, it delivers toxic FFA as an energy source to the myocardium (26). The role of EFT in CVD among uremic patients has recently

been investigated in several studies. In a study by Turkmen et al., the authors found a significant relationship between EFT volume and the presence of the malnutrition-inflammation-atherosclerosis calcification syndrome in HD patients (27). In another study by the same group, they reported a relationship between EFT and coronary artery calcification among peritoneal dialysis patients (17). In a recently published study by Turan et al, EFT volume was correlated with cardiovascular surrogate markers such as carotid intima-media thickness and pulse-wave velocity. However this did not reach statistical significance after adjusting for traditional risk factors such as BMI, age, cholesterol levels and systolic blood pressure (16). In our study, we also found higher EFT values measured by TTDE in HD patients when compared to healthy controls. Although many authors advise measuring EFT using multislice computerised tomography (MSCT) or magnetic resonance imaging (MRI), TTDE is a simple and inexpensive method for EFT measurement. In 2003, Iacobellis et al reported the echocardiographic measurement of EFT for the first time. They showed that EFT measurements with echocardiography were correlated with EFT measurements by MRI as well as anthropometric and metabolic parameters (24).

The present study evaluated EFT thickness in HD patients. EFT thickness was increased in HD patient population compared to healthy controls. In accordance with previous studies, we also found correlations between EFT and age, total cholesterol and BMI. Therefore based on these results, it can be postulated that atherosclerosis in the coronary vascular system starts in the early stages of uremia even when no clinical signs are present. Increased EFT is probably both a marker of atherosclerosis and a driving force for endothelial damage by producing proatherogenic cytokines in this patient population. Thus, EFT measurements can be used for assessing the atherosclerotic load of these patients at the very

beginning of the uremic state and may be used for detecting high risk patients for further interventions in order to decrease the high mortality rates seen in this patient group.

In the present study 8 patients in the dialysis group were on beta blocker treatment because of stable coronary artery disease in their patient history. Demographic characteristics and baseline laboratory parameters of this subgroup were not significantly different from the HD group. We also reported that 10 of 71 HD patients have ACE inhibitor/ARB treatment in their hypertensive medication. There is no data about the effect of ACE inhibition on EFT in HD patients in the literature. According to the results of the subgroup analysis, ACE inhibition did not affect EFT in HD patients. However, the present subgroup analysis is insufficient to interpret the effects of ACE inhibitor/ARB treatment due to the low number of patients.

This study has several limitations. First, since EFT has a three dimensional distribution, two dimensional echocardiographic measurements may not be enough to assess the total amount of EFT. Further studies are needed to compare MSCT, MRI and echocardiographic EFT measurements. Secondly, the design of the study is unable to define the importance of increased EFT in terms of mortality. Thus, prospective long-term studies are needed. Finally, these results should be interpreted with caution because of the small number of patients and further studies are needed to shed more light on this issue.

In conclusion, this study showed that EFT was increased and inversely correlated with CFR in HD patients. Further studies are needed to evaluate the role of EFT in CVD and find treatment strategies to decrease EFT volume.

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