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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 $\pm$ 13 years and time on hemodialysis 75 $\pm$ 44 months. Twenty percent of the patients had diabetes. Mean EAT volume was 62.6 $\pm$ 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 $\leq$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.