Relationship Between Epicardial Adipose Tissue and Body Composition as Determined by Multi-Frequency Bioelectrical Impedance Analysis in Patients with Stage 5 Chronic Kidney Disease

Background: The main cause of mortality among chronic kidney disease (CKD) patients is cardiovascular disease (CVD). Epicardial adipose tissue (EAT) is considered to be a novel cardiovascular risk factor. We assessed EAT in non-dialyzed stage 5 CKD patients and explored the association of EAT with body composition as determined by multi-frequency BIA.

Material/Methods: The present included 70 stage 5 CKD patients who had not undergone dialysis and 40 healthy control subjects. EAT thickness was assessed by echocardiography. Hydration status and body composition were evaluated by multi-frequency bioelectrical impedance analysis.

Results: Stage 5 CKD patients had significantly higher EAT thickness than healthy subjects (6.56±1.18 vs. 4.05±1.45, p<0.001). Fat tissue mass, systolic blood pressure (SBP), age, fat tissue index, and body mass index were positively correlated with EAT thickness in the CKD patient group (p<0.05). Lean tissue mass, lean tissue index (LTI), and high-density lipoprotein (HDL) were negatively correlated with EAT thickness in the CKD patient group (p<0.05). Stepwise multiple regression analysis showed that age, SBP, and LTI were independently associated with EAT thickness in CKD patients.

Conclusions: We found significantly higher EAT thickness in stage 5 CKD patients who were not on dialysis compared to healthy controls. EAT was significantly associated with age, SBP, and LTI in CKD patients. Interventions to reduce the risk factors associated with EAT thickness might protect against CVD disease in CKD patients.

MeSH Keywords: Adipose Tissue • Body Composition • Renal Insufficiency, Chronic

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Background

The worldwide prevalence of chronic kidney disease (CKD) is increasing in accordance with the global epidemic of diabetes mellitus and hypertension, and has become an important public health issue. According to the United States Renal Data System, the prevalence of CKD is about 15%, with exceedingly high associated costs [1].

CKD has deleterious effects on almost all organs and systems, particularly on the cardiovascular system. Heart disease is recognized as one of the most frequent complications and leading causes of mortality among CKD patients. Cardiovascular disease (CVD) causes almost half of all deaths in end-stage renal disease (ESRD) patients, and mortality from CVD is about 10–30 times greater in those patients than in the general population [2]. It is important to discover why CVD incidence and mortality rates are so much higher in CKD patients. Because conventional risk factors such as dyslipidemia, hypertension, and diabetes mellitus are insufficient to explain high CVD incidence rates in CKD patients, non-traditional risk factor such as endothelial dysfunction oxidative stress and inflammation might have substantial roles [3,4], and new cardiovascular risk factors need to be explored in this regard.

Epicardial adipose tissue (EAT) is the heart visceral fat tissue. It accounts for 20% of total heart weight, and approximately 80% of the cardiac surfaces are covered by EAT [5–7]. EAT has recently been considered to be a novel cardiovascular (CV) risk factor among patients with ESRD [8,9] and in non-uremic patients (7). EAT has unique features and acts like a very active organ that can generate adipokines and proinflammatory and proatherosclerotic cytokines [10–12]. Various studies have reported that EAT is associated with atherosclerosis and coronary artery calcification [13–15]. A significant relationship of EAT with mortality and risk of CV events has been demonstrated in recent studies [16,17]. However, very few studies have investigated EAT and relevant clinical and laboratory characteristics in non-dialyzed patients with CKD [17–19]. Thus, further studies are needed in this field.

Multi-frequency bioelectrical impedance analysis (BIA) can provide information about body fluid status and fat composition by measuring 50 different frequencies between 5 and 1000 kHz. The following data were obtained for body composition: resting and hydration status in supine position after a 5-min rest. The following data were obtained from the right arm by a sphygmomanometer after 5 min of resting. In this study, the 4-variable Modification of Diet in Renal Disease formula was used to assess estimated glomerular filtration rate (GFR; mL/min per 1.73 m² body surface area) [20]. Stage 5 CKD patients were identified according to Kidney Disease Outcomes Quality Initiative (K/DOQI) classification (estimated GFR lower than 15 mL/min/1.73 m²) [21]. Blood specimens were taken for hematological, serological, biochemical, and hormonal evaluation after 12 h of fasting.

Bioelectrical impedance analysis

A multi-frequency BIA device (Fresenius Medical Care D GmbH, Body Composition Monitor) was used to assess body composition and hydration status in supine position after a 5-min rest. The following data were obtained for body composition: total body water (TBW, lt), extracellular water (ECW, lt), cell water (CW, lt), intracellular water (ICW, lt), extracellular water (ECW, lt), overhydration (OH, lt), body fat mass index (BMI), lean tissue mass (LTM, kg), and lean tissue index (LTI, LTM/height²; kg/m²).

Material and Methods

This cross-sectional study included 70 patients with stage 5 CKD who had not undergone dialysis (37 men, 33 women; mean age 48.70±15.65 years) at the Nephrology Clinic of Dicle University Medical Faculty Hospital and 40 healthy control subjects (24 men, 16 women; mean age 45.55±11.45 years).

Healthy subjects were those who went to the outpatient clinic for a check-up and had no disease detected. Exclusion criteria were: (1) undergoing dialysis treatment, (2) history of CVD or congestive heart failure, (3) malignancy, cerebrovascular disease, sepsis, or pregnancy (4) hemodynamically unstable, and (5) metallic intravascular devices, limb amputation, or pacemakers. The etiologies of CKD patients were: hypertension (n=28, 40%), diabetes mellitus (n=22, 32%), chronic glomerulonephritis (n=11, 15%), postrenal cause (n=1, 1%), polycystic kidney disease (n=1, 1%), and undetermined (n=7, 10%). Initially, 85 patients with stage 5 CKD met the inclusion criteria. However, 8 of 15 patient did not want to participate in the study and EAT was not well measured in 7 of 15 patients due to technical issues. Thus, we included 70 patients with stage 5 CKD in our study design. The Non-Invasive Clinical Research Ethics Committee of Dicle University Medical School approved the design of the study (Decision number 191, Date: 19.09.2018).

All the performed procedures were complied with the 1964 Helsinki Declaration. All participants provided informed consent.

Clinical characteristics and demographic of all patients were recorded. We measured the body mass index (BMI) of the patients through dividing weight (kg) by the square of the height (centimeters). Blood pressures reading were obtained from the right arm by a sphygmomanometer after 5 min of resting. In this study, the 4-variable Modification of Diet in Renal Disease formula was used to assess estimated glomerular filtration rate (GFR; mL/min per 1.73 m² body surface area) [20]. Stage 5 CKD patients were identified according to Kidney Disease Outcomes Quality Initiative (K/DOQI) classification (estimated GFR lower than 15 mL/min/1.73 m²) [21]. Blood specimens were taken for hematological, serological, biochemical, and hormonal evaluation after 12 h of fasting.
Echocardiographic evaluation of epicardial adipose tissue thickness

The EAT thickness of all patients and control subjects was examined by two-dimensional M mode echocardiography (Vivid 7, GE Healthcare, Horten, Norway) with a 3.5-MHz transducer. All echocardiographic examinations were performed by the same cardiologist.

The echo-free space among the pericardial layers at echocardiographic examination was assessed as EAT. We measured the thickness of EAT on the free wall of the right ventricle at end-diastole from parasternal short- and long-axis views [22]. EAT was examined at 3 cardiac cycles, and the mean value was used.

Statistical analyses

Data were analyzed using SPSS version 20.0 for Windows. Visual (probability plots, histograms) and analytical (Kolmogorov-Smirnov test) methods were used to evaluate the normal distribution of variables. The mean values of the variables with normal distribution were compared by t test. Variables with normal distribution were analyzed using Pearson correlation analysis for CKD patients. The chi-square test was applied in the analysis of categorical variables. The independent variables of EAT in CKD patients were demonstrated by using stepwise multiple linear regression analysis. The data are shown as mean±standard deviations, and p<0.05 was considered significant.

Results

We enrolled 70 stage 5 CKD patients who were not undergoing dialysis and 40 healthy control subjects. Age and sex were not significantly different between the CKD patient group and the control group. SBP (135.13±24.90 vs. 124.76±17.68, p=0.014), DBP (88.32±22.56 vs. 73.16±9.82, p=0.044), creatinine (6.08±2.06 vs. 0.78±0.13, p<0.001), and C-reactive protein (3.16±0.75 vs. 1.77±0.44, p=0.124) levels were significantly higher, while BMI (23.48±4.02 vs. 27.34±5.06, p<0.001), albumin (2.71±0.65 vs. 4.19±0.25, p<0.001), hemoglobin (10.75±1.91 vs. 14.75±1.47, p<0.001), and high-density lipoprotein (HDL) (36.42±9.95 vs. 43.34±10.34, p=0.001) levels were significantly lower in stage 5 CKD patients than in controls. EAT thicknesses were significantly higher in stage 5 CKD patients than in healthy subjects (6.56±1.18 vs. 4.05±1.45, p<0.001; Figure 1). Data on demographic and clinical features, laboratory results, and echocardiographic results are shown in Table 1.

Compared to healthy subjects, stage 5 CKD patients had significantly higher levels for TBW (37.21±8.75 vs. 34.86±6.44, p=0.028), ECW (16.74±4.48 vs. 15.40±3.44, p=0.003), OH (1.63±0.55 vs. 0.41±0.15, p<0.001), and OH/ECW (7.99±1.54 vs. 3.35±1.48, p<0.001). Comparison of BIA-derived parameters for the groups are presented in Table 2.

Age (r=0.801, p<0.001), SBP (r=0.786, p<0.001), BMI (r=0.409, p<0.001), FTM (r=0.848, p<0.001), and FTI (r=0.556, p<0.001; Figure 2A) were positively correlated with EAT in the CKD patient group. However, HDL (r=−0.249, p=0.039), LTM (r=−0.499, p<0.001), and LTI (r=−0.793, p<0.001; Figure 2B) were negatively correlated with EAT in the CKD patient group. Table 3 depicts the correlation analysis of EAT and study parameters in the CKD patient group.

In addition, we applied stepwise multiple regression analysis for determining independent variables of EAT in the CKD patient group. Age, SBP, BMI, HDL, FTM, and LTI were included into the model. Age, SBP, and LTI were only independently associated with EAT thickness (R²=0.764, p<0.001, Table 4). BMI, FTM, and HDL were not independently associated with EAT thickness in stepwise multiple regression analysis.

Discussion

The present study has 3 main findings. First, EAT thickness was significantly higher in stage 5 CKD patients who had not yet undergone dialysis treatment than in healthy subjects. Second, EAT thickness was positively associated with FM and FMI and was negatively associated with LTM and LTI in CKD patients as determined by BIA. Third, age, SBP, and LTI were independent predictors of EAT thickness in CKD patients.

EAT is exclusively visceral fat tissue of the heart, which is located between the myocardium and the visceral pericardium, and is also a metabolically active paracrine and vasocoric organ [23,24]. During the past 10 years, numerous studies have focused on the association of EAT with cardiovascular disease...
and risk. However, few studies have assessed EAT and its relevance in ESRD patients, especially in non-dialyzed CKD patients. To the best of our knowledge, this is the first study to investigate the relationship between EAT and body fat composition as determined by multi-frequency BIA in non-dialyzed patients with stage 5 CDK.

**Table 1.** Comparison of the groups according to demographic, clinical, laboratory, and echocardiographic characteristics.

| Parameters                        | Stage 5 CKD (n=70) | Control (n=40) | P     |
|-----------------------------------|--------------------|----------------|-------|
| Age (years)                       | 48.70±15.65        | 45.55±11.45    | 0.238 |
| Sex (Male/Female)                 | 37/33              | 24/16          | 0.425 |
| BMI (kg/m²)                       | 23.48±4.02         | 27.34±5.06     | <0.001|
| SBP (mmHg)                        | 135.13±24.90       | 124.76±17.68   | 0.014 |
| DBP (mmHg)                        | 88.32±22.56        | 73.16±9.82     | 0.044 |
| Creatinine (mg/dl)                | 6.08±2.06          | 0.78±0.13      | <0.001|
| GFR (ml/min/1.73 m²)              | 9.78±2.08          | 97.58±17.63    | <0.001|
| Albumin (g/dl)                    | 2.71±0.65          | 4.19±0.25      | <0.001|
| CRP (mg/dl)                       | 3.16±0.75          | 1.77±0.44      | 0.124 |
| Hemoglobin (g/dl)                 | 10.75±1.91         | 14.75±1.47     | <0.001|
| Triglycerides (mg/dl)             | 164.87±69.09       | 166.61±113.20 | 0.932 |
| Total cholesterol (mg/dl)         | 173.52±57.68       | 187.55±38.87   | 0.138 |
| LDL cholesterol (mg/dl)           | 121.00±41.99       | 116.29±30.75   | 0.509 |
| HDL cholesterol (mg/dl)           | 36.42±9.95         | 43.34±10.34    | 0.001 |
| Ca×P (mg²/dl²)                    | 36.27±9.03         | 24.69±50.76    |       |
| PTH (pg/ml)                       | 58.84±5.98         | 60.00±10.00    | 0.112 |
| EF (%)                            | 6.56±1.18          | 4.05±1.45      | <0.001|

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; GFR – glomerular filtration rate; CRP – C-reactive protein; LDL – low-density lipoprotein, HDL – high-density lipoprotein; PTH – parathyroid hormone; Ca – calcium; P – phosphate; EF – ejection fraction; EAT – epicardial adipose tissue. t test.

**Figure 2.** (A) EAT thickness was positively correlated with FTI. (B) EAT thickness was negatively correlated with LTI.
It has been shown in several studies that EAT thickness is increased in CKD patients. Several studies showed significantly higher levels of EAT thickness in hemodialysis (HD) patients than in healthy subjects [14,25–27]. In another study, including 120 patients with CKD and 30 control subjects, Sheng et al. observed that patients with stage 4–5 CKD had significantly higher epicardial fat volume as measured by computed tomography than in control subjects [18]. In agreement with the findings of these previous reports, we found significantly higher EAT thickness in non-dialyzed stage 5 CKD patients compared to control subjects. In the present study, systolic blood pressure was positively correlated with EAT thickness in CKD patients. Furthermore, we found that SBP was independently associated with EAT thickness in CKD patients. The relationship between the epicardial fat and left ventricular mass has been previously reported [17]. The prevalence of hypertension (HT) is high among ESRD patients. One of the mechanisms that might explain this relationship is that elevated blood pressure leads to increased left ventricular wall thickness; therefore, EAT mass increases to meet the growing myocardial energy requirement.

### Table 2. Comparison of BIA-derived parameters for the groups.

| Parameters | Stage 5 CKD (n=70) | Control (n=40) | P   |
|------------|-------------------|----------------|-----|
| TBW (lt)   | 37.21±8.75        | 34.86±6.44     | 0.028|
| ECW (lt)   | 16.4±4.48         | 15.40±3.44     | 0.003|
| ICW (lt)   | 20.48±6.67        | 19.60±3.63     | 0.322|
| OH (lt)    | 1.63±0.55         | 0.41±0.15      | <0.001|
| OH/ECW%    | 7.99±1.54         | 3.35±1.48      | <0.001|
| FTM (kg)   | 30.58±11.03       | 29.47±6.69     | 0.520|
| LTM (kg)   | 35.21±10.40       | 37.42±11.08    | 0.317|
| FTM (kg/m²)| 10.25±3.31        | 10.98±2.37     | 0.190|
| LTM (kg/m²)| 12.28±3.54        | 13.59±3.50     | 0.093|

TBW – total body water; ECW – extracellular water; ICW – intracellular water; OH –overhydration; FTM – fat tissue mass; LTM – lean tissue mass; FFI – fat tissue index; LTI – lean tissue index. t test.

### Table 3. Correlations between study parameters and EAT thickness in the stage 5 CKD patient group.

| Variable | r   | p     |
|----------|-----|-------|
| Age      | 0.801 | <0.001 |
| SBP      | 0.786 | <0.001 |
| DBP      | 0.005 | 0.970 |
| BMI      | 0.409 | <0.001 |
| Total cholesterol | 0.170 | 0.163 |
| Triglycerides | 0.112 | 0.361 |
| LDL      | 0.152 | 0.211 |
| HDL      | 0.249 | 0.039 |
| Creatinine | 0.037 | 0.761 |
| CRP      | 0.242 | 0.052 |
| Ca×P     | 0.070 | 0.578 |

| Variable | r   | p     |
|----------|-----|-------|
| PTH      | 0.064 | 0.612 |
| Albumin  | 0.031 | 0.803 |
| Hgb      | 0.018 | 0.883 |
| OH       | 0.024 | 0.846 |
| TBW      | 0.213 | 0.079 |
| ECW      | 0.193 | 0.027 |
| ICW      | 0.167 | 0.169 |
| OH/ECW   | 0.009 | 0.939 |
| FTM      | 0.848 | <0.001 |
| FFI      | 0.556 | <0.001 |
| LTM      | 0.499 | <0.001 |
| LTI      | 0.793 | <0.001 |

SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; LDL – low-density lipoprotein, HDL – high-density lipoprotein; CRP – C-reactive protein; Ca – calcium; Hgb – hemoglobin; P – phosphate; PTH – parathyroid hormone; OH –overhydration; TBW – total body water; ECW – extracellular water; ICW – intracellular water; FTM – fat tissue mass; FFI – fat tissue index; LTM – lean tissue mass; LTI – lean tissue index. Pearson correlation analysis.

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Table 4. Stepwise multiple linear regression analyses for the independent determinants of EAT thickness in the stage 5 CKD patient group.

| Independent variables | Beta coefficient | 95% CI       | Standardized Beta coefficient | P     |
|-----------------------|------------------|--------------|-------------------------------|-------|
| Age                   | 0.025            | 0.01 to 0.041| 0.333                         | 0.002 |
| SBP                   | 0.016            | 0.007 to 0.025| 0.330                         | 0.001 |
| LTI                   | -0.034           | -0.168 to -0.033| -0.300                        | 0.004 |
| Constant              | 4.453            |              |                               |       |

CI – confidence interval. Model: p<0.001; R^2=0.764. Included variables in the model were BMI, FTI, HDL, age, SBP, and LTI. Out of the model: BMI (p=0.643), FTI (p=0.214), and HDL (p=0.290). BMI – body mass index; FTI – fat tissue index; HDL – high-density lipoprotein; SBP – systolic blood pressure; LTI – lean tissue index. Stepwise multiple linear regression analysis.

Dyslipidemia is a conventional risk factor for development of CVD. HDL levels are usually reduced and triglyceride levels are elevated in ESRD patients. Turan et al. revealed an independent association between total cholesterol levels and EAT [8]. Erdur et al., in a cross-sectional study that included 76 ESRD patients who were on hemodialysis or peritoneal dialysis treatment, observed that the logarithmic ratio of triglycerides to HDL was significantly associated with EAT [28]. Similar to the results of Erdur et al., we observed a negative association between HDL and EAT thickness.

It is well-accepted that changes in body fluid and fat composition occur in CKD patients. Decrease in muscle mass, which is good indicator of malnutrition, is proposed as one of the diagnostic criteria for protein-energy wasting in CKD patients [29]. Oxidative stress, nonspecific inflammation, uremic toxins, insulin resistance, metabolic acidosis, protein-restricted diet, and vitamin D deficiency are common metabolic disorders in patients with CKD, and can lead to decrease in muscle mass [30]. Currently, to the best of our knowledge, only 1 study has investigated the association between EAT and body fat in HD patients, as assessed by BIA; in this cross-sectional study, Okyay et al. [31] found a positive correlation between EAT with BFM and percentage of BFM and a negative correlation with percentage of LTM. They also showed that BFM and percentage of LTM were independently associated with EAT thickness. We also used bioimpedance analysis for evaluating the body composition of participants in the present study, and, similar to the results of Okyay et al., we observed that EAT thickness was positively associated with FM and FMI and negatively associated with LTM and LTI in CKD patients. Our multiple stepwise linear regression analysis found that LTI is an independent predictor of EAT thickness in CKD patients.

Previous studies have shown that older age and increased BMI were significantly associated with EAT [8,14,16,32]. Our results also confirmed these previous studies by demonstrating that age and BMI were significantly positively correlated with EAT thickness, and that age was an independent predictor of EAT thickness in multivariate analysis. Obesity is a critical factor for cardiovascular disorders, and BMI is significantly associated with EAT thickness in ESRD patients [32]. Muscle mass gradually decreases with age, especially after the fourth decade of life [33]. This decrease in muscle mass with aging is more pronounced in CKD patients than in healthy subjects due to the adverse effects of metabolic disorders in CKD patients, as detailed previously [30,34–36]. The close relationship between the age and EAT thickness might be attributable to changes in body composition along with aging.

Interestingly, we did not find any relationship between hydration status and EAT as assessed by BIA. The present study has some limitations. First, this was a cross-sectional study with a relatively small sample size in stage 5 CKD patients. Second, BIA is not a criterion standard method for body composition analysis; however, it is non-invasive, safe, and validated method for this purpose. Third, there was patient variability.

Conclusions

In conclusion, we found significantly higher EAT thickness in stage 5 CKD patients who were not on dialysis compared to healthy controls. We also found a significant association between LTI and EAT as determined by multi-frequency BIA in CKD patients. Nevertheless, further studies are needed to confirm this association. Interventions to reduce the risk factors associated with EAT thickness might protect against CVD disease in CKD patients, but our study did not evaluate this effect.

Conflict of interest

None.
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