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Epicardial Adipose Tissue Volume As A Marker of Atherosclerosis in Hemodialysis Population.

Vivek Praveen R[1],Suhasini B[2],Edwin Fernando M[3],Srinivasaprasad Nd[4]
Departments of Nephrology &Radiodiagnosis,Govt. Stanley Medical College, Chennai.

Backround: *Epicardial adipose tissue (EAT) is a visceral fat deposit accumulated between the visceral pericardium and the myocardium. Increased epicardial adipose tissue volume is associated with development of coronary atherosclerosis. It has been reported previously that EAT volume was higher in Chronic Kidney Disease (CKD) patients on hemodialysis(HD) and peritoneal dialysis.*

Objective: *We aimed to compare epicardial adipose tissue thickness between the CKD patients on hemodialysis and controls.*

Materials And Methods*: Thirty patients on HD (16 males & 14 females, with a mean age of 41.97± 9.77 yrs) and thirty controls (12 males & 18 females, with a mean age of 46.93±7.27yrs) were enrolled in the study. Carotid intimal medial thickness (CIMT), Coronary artery calcification score (CACS), EAT thickness and volume were measured by appropriate imaging techniques.*

Results: *E.A.T volume is increased in 20% (6 out of 30) of cases and 16.67% (5 out of 30) of controls. Mean E.A.T volumes in cases were 97.83 cc (±26.11) and in controls were 97.87 cc (± 28.53).No statistical significant differences noted in E.A.T volume between cases and controls.*

Mean CACS for cases and controls were 0.4(± 0.81) and 0.27(±0.69) respectively. No statistically significant difference noted. Mean CIMT (right) for cases and controls were 0.57mm (±0.1) and 0.57mm (±0.08) respectively. Mean CIMT (left) for cases and controls were 0.59mm (±0.13) and 0.58mm (0.10) respectively. No statistically significant difference noted.

No significant association was noted between age,BMI,Triglycerides, CIMT, CACS, with EAT volume in CKD patients on hemodialysis.However there is significant positive correlation between E.A.T thickness measured using echocardiography versus CT (r=0.94, p<0.05).

Conclusions

The main findings of the present study are as follows:

1) *E.A.T volume measured by CT is not increased in most of the CKD patients on HD.*

2) *No significant correlation found between E.A.T volumes with other parameters (Age, BMI, TGL, dialysis vintage, CACS, CIMT) in CKD patients on HD.*

3) *Significant positive correlation between E.A.T thicknesses measured using echocardiography and CT.*

In recent studies, a preferential association between E.A.T volume and thickness is made with CACS, CIMT. However we found no association.

Our study has some limitations.

1) *Sample size was relatively small.*

2) *Dialysis vintage was relatively short.*

3)*Since this is not a prospective study, we cannot draw cause and effect relation.*

Keywords: Hemodialysis, epicardial adipose tissue, coronary artery calcification, Carotid intimal medial thickness, Chronic Kidney Disease.

I. Introduction

Cardiovascular diseases are the most common cause of death in CKD patients on hemodialysis[(1).] Cardiovascular disease in CKD patients is associated with atherosclerosis, endothelialdysfunction, coronary artery calcification, and left ventricular hypertrophy.The CIMT and CACS are markers of atherosclerotic vascular disease and predicts cardiovascular events in CKD patients [(4,5).]Multidetector computerised tomography (MDCT) is non-invasive test to quantify CACS [(6,7).]Recent studies have shown an association between CACS and atherosclerosis in CKD populationEpicardial adipose tissue (EAT) is the true visceral fat deposit of the heart that accounts for approximately 20% of the total heart weight and covers 80% of the cardiac surface[(8,9).]Recent studies used MDCT and echocardiography to measure EAT thickness.[(10,11)]There exist close relationship between CAD and EAT[(12,13)] MDCT is also useful in measuring EAT volume. In the literature, to date there are not enough data regarding EAT in ESRD patients. Therefore, in the present study we aimed to investigate,

1)Epicardial adipose tissue volume measurement using CT in CKD patients on hemodialysis and in controls

2) Association of epicardial adipose tissue volume with coronary artery calcification score (CACS) and carotid intimal medial thickness (CIMT).
3) Association of epicardial adipose tissue volume with age, BMI, dialysis vintage, lipid profile.
4) Comparison of epicardial adipose tissue thickness measured using two different modalities (CT Vs Transthoracic echocardiography).

Patients and methods:

This is a cross sectional study involving patients with ESRD receiving HD for at least 3 months in outpatient hemodialysis unit of Stanley Medical College,Chennai.ThirtyESRD patients receiving HD between ages 18 to 58 years were taken as subjects. Thirty prospective renal donors between ages 18 to 58 year acted as controls.Patients with active infection, autoimmune disease, cardiac failure, hypothyroidism and history of chronic smoking were excluded. Patient's demographic data, medications, primary disease of ESRD and dialysis duration were recorded. Systolic and diastolic blood pressure of both cases and controls were measured in an upright sitting position after at least 5 min of rest using sphygmomanometer with an appropriate cuff size. The study protocol was approved by the institutional medical ethics committee and written informed consent was obtained from all subjects included in the study.

Biochemical analysis:

Fasting blood glucose, total cholesterol, triglyceride, urea, creatinine, haemoglobin, albumin, calcium, phosphorus were measured for cases and controls in our renal laboratory.

CIMT, CACS And EAT Measurement: CIMT was measured with USG instrument (ACUVIX XG) according to standard techniques, with subjects in supine position. Linear probe (7.5-12 MHz) was manipulated manually so as to run parallel to the common carotid artery. A region 4cm proximal to the carotid bifurcation (right & left) was identified, and the intimal – medial thickness of the far wall was calculated as distance between the lumen intima and media adventitia interfaces.

Cardiac CT scans were done using 128 slice MDCT (Optima CT6600, GE health care); axial images of 0.625 mm slice thickness were obtained. Multiplanar data reconstruction was obtained in standardised ventricular short axis plane and the horizontal long axis plane from root of aorta to base of heart. To quantify CACS, all reconstruction was transferred to a PC based workstation (GE Advantage workstation). CACS was defined as the presence of more than two contiguous pixels with Hounsfield units greater than 130, which was designed by Agatston et al. [6]. All values of the left anterior descending coronary artery (LAD), circumflex coronary artery (Cx), and right coronary artery (RCA) were added to calculate the calcium scores. To quantify the epicardial fat volume, all reconstructions were transferred to a PC-based workstation (GE Advantage workstation). A CT attenuation threshold between −200 and −20 Hounsfield units was used to isolate the epicardialfat.EAT thickness using CT measured over right ventricular free wall during diastole in a four chamber view.EAT thickness using echo scan was measured using USGinstrument(ACUVIX XG) according to standard technique, with subjects lying on their left side, with the left arm widely abducted small footprint probe (2.5-6 MHz) was used and thickness measured over right ventricular free wall during diastole in four chamber view.

II. Statistical Analysis

Statistical analysis was carried out by the statistical package for social sciences for windows ver.20.0 .Datas were expressed as the mean± SD, with a significance level of $p < 0.05$. ForDichotomous variables, the frequency of positive occurrences was given along with their corresponding percentages. Statistical comparisons of individual groups were based on Student's t test for continuous variables, whereas the correlations between groups were evaluated by Pearson's test. Significant determinants identified from univariate analysis were studied in a stepwise multiple regression model.ANCOVA (general linear model) was used to determine the relationship between PD and EAT after the correction of variables on EAT.

III. Results

The baseline characteristics of the 30 HD patients and 30 controls are depicted in Table 1.The etiology of the thirty cases are IgA nephropathy (n= 2), Reflux nephropathy (n=2), FSGS (n=1), Alport's syndrome (n=1), vasculitis (n=1), unknownetiology (n=23).No significant difference in age, gender, BMI between HD patients and controls. Howeversignificant difference inSBP,DBP,FBS,Hb,TC,TGL,Albumin,calcium,phosphorus,LVEF were noted.

Table 1: Demographic And Laboratory Features Of The Hd Patients And Controls

	Controls N =30	Cases N =30	P value
Characteristics			
Age, Years	46.73±7.27	41.97±9.77	NS
Male/Female	12/18	16/14	NS
BMI	20.64 ± 0.71	19.74 ± 1.13	0.001
SPB, Mm Hg	117.73±5.24	158.73±11.61	<0.001
DPB, Mm Hg	78.87±2.87	94±6.5	<0.001
Laboratory Data			
Haemoglobin,g/dl	10.78±1.12	9.04±0.52	<0.001
FBS,mg/dl	96.87±8.22	91.27± 6.23	0.004
TC,mg/dl	169.47±16.99	190.27±14.62	<0.001
TGL,mg/dl	118.93±21.58	144.47±14.93	<0.001
Albumin,mg/dl	4.92±0.33	3.56±0.25	<0.001
Calcium,mg/dl	9.97±0.29	7.95±0.28	<0.001
Phosphorus,mg/dl	3.75±0.44	5.86±0.25	<0.001
LVEF,%	61.83±2.45	48±6.1	<0.001
CIMT RT, mm	0.57±0.07	0.57±0.1	NS
CIMT LT, mm	0.58±0.1	0.58±0.13	NS
CACS	0.27±0.69	0.4±0.8	NS
Echo,EAT,mm	3.58±0.95	3.47±0.93	NS
CT,EAT,mm	3.48±1.06	3.25±1.06	NS
CT,EAT,cc	97.87±28.52	97.83±26.11	NS

Values are mean ± SD.BMI-Body mass index, SBP-Systolic blood pressure,DBP- Diastolic blood pressure,FBS- Fasting blood sugar,TC – Total cholesterol,TGL-triglycerides,LVEF- Left ventricular ejection fraction, CIMT-Carotid intimal medial thickness ,RT-right,LT-left,CACS-Coronary artery calcification score, EAT-Epicardial adipose tissue,CT-computerised tomography.p value <0.05 significant.

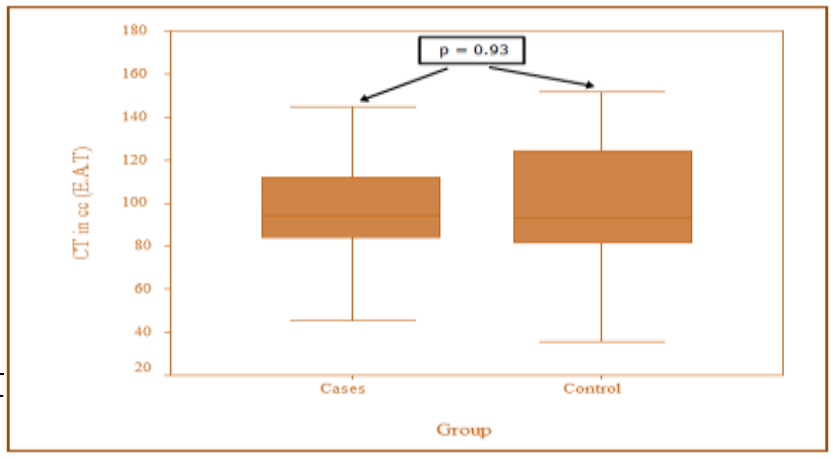
CIMT and CACS Measurement:

Mean CACS for cases and controls were 0.4(± 0.0.81) and 0.27(±0.69) respectively. No statistically significant difference noted. Mean CIMT (right) for cases and controls were 0.57mm (±0.1) and 0.57mm (±0.08) respectively. Mean CIMT (left) for cases and controls were 0.59mm (±0.13) and 0.58mm (0.10) respectively. No statistically significant difference noted.

EAT Measurement:

E.A.T volume is increased in 20% (6 out of 30) of cases and 16.67% (5 out of 30) of controls. Mean E.A.T volume in cases was 97.83 cc (±26.11) and in controls were 97.87 cc (± 28.53). No statistical significant differences noted in E.A.T volume between cases and controls. (Figure 1)

Figure 1: Relation Between Eat Values In Cases And Controls



Correlation is significant at the p value < 0.05 level.
EAT-Epicardialadipose tissue.
Increased EAT > 125 cc

In the univariate correlation analysis, EAT was not correlated with age, BMI, CIMT, CACS, TC, TGL. (Table 2)

Table 2: Univariate Correlation Analysis

Parameters	**Correlation Coefficient,r**	**P Value**
Age ,Years	0.147	0.438
BMI	0.136	0.475
TC,mg/dl	0.035	0.856
TGL,mg/dl	-0.003	0.988
LVEF%	-0.08	0.674
CIMT,RT,mm	-0.08	0.673
CIMT,LT,mm	0.11	0.562
CACS	-0.05	0.785
ECHO,EAT,mm	0.872	<0.001
CTP,EAT,mm	0.839	<0.001
Dialysis Vintage, Months	-0.185	0.328

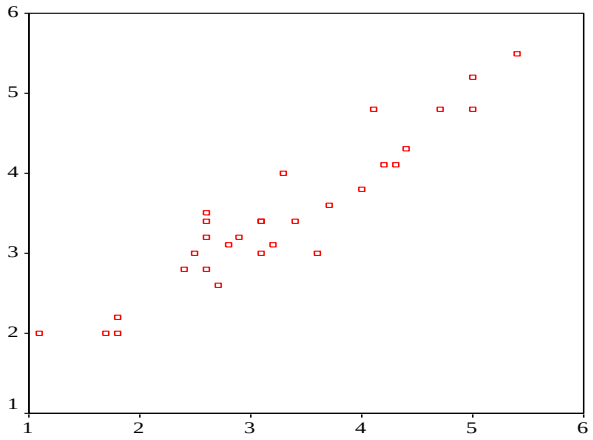
We performed a linear regression analysis to define the variables of increased EAT. Age, BMI, CIMT, CACS, TC, and TGL were included in this model.According **t**o the linear regression analysis,age, BMI, TGL, LDEF, CIMT, CACS, Dialysis vintage did not correlate with increased EAT (Table 3)

Table 3: Variables Of Eat

PARAMETERS	**Standardized ß**	**t**	**P value**
Age ,years	0.212	0.81	0.42
BMI	0.083	0.33	0.74
TGL,mg/dl	-0.155	-0.62	0.54
LVEF %	-0.057	-0.27	0.79
CIMT,RT,mm	-0.073	-0.29	0.77
CIMT,LT,mm	0.096	0.39	0.69
CACS	-0.083	-0.83	0.72
Dialysis vintage, months	-0.269	-0.27	0.29

In the univariate covariance analysis(ANCOVA), the HD modality was not associated with increased EAT volume when corrected for age and BMI (t=0.35, p=0.93).EAT thickness measured in HD patients using echocardiography 3.47 mm (± 0.93) versus CT 3.25 mm (± 1.06).Paired sample test showed significant positive correlation between EAT thickness in HD patients measured using echocardiography and CT. (r=0.94, p<0.05). (FIGURE 2)

Figure 2: correlation between eat thickness in cases measured using echocardiography and ct.



IV. Discussion

The main findings of the present study are as follows.

1) EAT volume measured by CT is not increased in most of the CKD patients on HD.

2) No significant difference between EAT volume in HD patients and controls.

3) No significant correlation found between E.A.T volumes with other parameters (Age, BMI, TGL, dialysis vintage, CACS, CIMT) in CKD patients on HD.

4) Significant positive correlation between E.A.T thicknesses measured using echocardiography and CT.

To our knowledge, this is the first study to compare EAT thickness in HD patients between echocardiography and CT.The most common cause of death in CKD patients on hemodialysis is cardiovascular disease. This can be due to many factors like old age, accelerated atherosclerosis, uncontrolled hypertension, anemia, secondary hyperparathyroidism, endothelial dysfunction, LVH, vascular calcification. Carotid intimal medial thickness is a marker of atherosclerosis. Coronary artery calcification is a part of extended vascular calcification. [(14)]Clinical studies have shown that EAT quantity correlates with coronary atherosclerosis and cardiovascular disease in CKD population[(15, 16, 17).]However in studies showing a positive association between EAT quantity and CACS, the EAT quantity was not related to CACS severity in ESRD [(18, 19)].

In our study no significant correlation found between EAT volume with age,BMI,totalcholesterol,TGL,dialysisvintage,CIMT,CACS.

EAT originates from splanchonopleuric mesoderm[(20)].EAT is metabolically active tissue and it secretes proinflammatory cytokines and utilizes free fatty acids under ischemic condition, EAT provides free fatty acid to the myocardium [(21).] Under normal condition EAT act as shock absorber and scavenges excess free fatty acids [(14).] In CKD patient on hemodialysisproinflammatory cytokines are generally increased and associated with atherosclerosis CIMT, CACSThe effect of intradialytic exercise training on oxidative stress and EAT (determined by echocardiography) was studied by Wilandet.al[(24)].He found that EAT thickness reduced by 11% in patients with intradialysisexercisetraining. So exercise training might improve cardiovascular disease risk factors (EAT).We measured EAT thickness using echocardiography and CT.We found significant positive correlation between EAT thickness measured using echocardiography and CT.Our study has some limitations. First, the sample size was relatively small.Second, the dialysis vintage was relatively short. Third, since this is not a prospective controlled study, we cannot draw cause and effect relationship.

In conclusion, we found that EAT is not significantly increased in ESRD patients on hemodialysis. Also no significant difference between EAT volumes in ESRD patients versus controls. Further large studies are needed to determine the relationship between EAT and other markers of atherosclerosis. Also to find out EAT volume in ESRD patients on hemodialysis.

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