Epicardial Adipose Tissue in Patients with End Stage Renal Disease on Haemodialysis

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Abstract

Purpose of review:

Epicardial adipose tissue (EAT) is the visceral fat of the heart, sharing many of the pathophysiological properties of other visceral fat depots. EAT is a metabolically active paracrine and vasocrine organ that causes local cardiac inflammation and is strongly implicated in the pathogenesis of coronary atherosclerosis. This article highlights the findings of recent observational studies in haemodialysis (HD) patients that link the quantity of EAT to increased rates of cardiovascular and coronary artery disease, reviews the proposed methods of pathogenesis and the possible role of EAT quantification to improve cardiovascular risk assessment.

Recent findings:

Increasing volumes of EAT in HD patients correlate with increased inflammatory mediators, higher rates of cardiovascular disease and coronary artery calcification, independent of general adiposity. EAT to be an independent predictor of mortality and is a potentially modifiable target for therapeutic interventions.

Summary:

EAT is likely to play a central role in the pathogenesis of cardiovascular disease in HD patients, adds incrementally to conventional cardiovascular risk stratification models and is a potential target for therapeutic intervention.

Keywords:

Epicardial adipose tissue, epicardial fat, haemodialysis, dialysis, cardiometabolic risk, coronary artery calcification

Introduction

Epicardial adipose tissue (EAT) is a metabolically active visceral fat deposit that covers 80% of the cardiac surface and accounts for approximately 20% of total cardiac weight. Like other white adipose tissues, EAT has endocrine functions with the ability to secrete hormones and inflammatory cytokines. The physiological function of EAT remains unclear, but is thought to include: regulation of local fatty acid homeostasis; provision of an immediate local energy source; assisting in coronary artery remodeling; and supporting coronary arteries against torsion from cardiac contraction and arterial pulse wave [1,2]. The expression and secretion of pro-inflammatory cytokines, such as interleukin-6 (Il-6), interleukin-1-beta (IL-1 β), monocyte chemo-attractant protein 1 (MCP-1) and tumour necrosis factor-alpha (TNF α) are higher in the EAT of patients with coronary heart disease than in subcutaneous fat of the same individuals, and the pathological enlargement of EAT correlates significantly with increased cardiovascular disease (CVD) risk [3,4]. The importance of EAT in relation to the inflammatory burden in CVD is established [5,6] with paracrine and vasocrine secretion of pro-inflammatory adipokines. Adipokines are thought to contribute directly to myocardial inflammation, left ventricular hypertrophy (LVH), coronary artery disease (CAD) and myocardial dysfunction through generation of local reactive oxygen species (ROS), creating a pro-atherogenic state and as a direct local effect of inflammatory cytokines [4,7]. Whilst obesity and body mass index (BMI) are commonly used and easily obtainable figures to stratify patients' cardiometabolic and atherosclerotic risk, they are far from perfect. There is good evidence from prospective, cross-sectional imaging and anthropometric studies that regional distribution of adipose tissue rather than an overall excess of body fat correlates with CVD and its associated risk [8-10]. Furthermore, the association between EAT and CAD has been shown to be independent of BMI and diabetic status [3].

EAT and its relevance in the pathogenesis of CVD amongst patients with end stage renal disease (ESRD) on haemodialysis (HD) is a relatively under researched area. Chronic kidney disease (CKD) is a chronic inflammatory condition, as evidenced by increased circulating levels of acute phase proteins

and pro-inflammatory cytokines, such as C-reactive protein (CRP), Il-6 and TNF- α [11]. Both inflammation and oxidative stress play central roles in the development of atherosclerosis in patients with CKD, and in functional CVD related outcomes, including pathogenesis of LVH, arterial stiffness and global cardiac function [12,13]. Recently the associations between increased EAT thickness, Il-6 and coronary artery calcification (CAC) in patients with CKD stage 3-5 [14] have been demonstrated. Additionally, increasing volumes of EAT in this patient population are associated with an increasing risk of cardiovascular events, independent of general adiposity, and are a better predictor of risk than abdominal visceral adipose tissue [15*]. This review summarises the role EAT may play in pathogenesis of CVD in patients on HD and whether imaging EAT may hold prognostic implications for cardiovascular events and mortality within this patient group.

Epicardial adipose tissue measurement

EAT can be measured in a number of different ways using different imaging modalities. The three commonly used methods are trans-thoracic echocardiography (ECHO), computerised axial tomography scanning (CT scanning) and cardiac magnetic resonance imaging (CMR). The relative strengths and weaknesses of these modalities are summarised in table 1. CMR and CT are three dimensional imaging techniques which allow calculation of total EAT volume whereas ECHO is primarily a two dimensional technique. Although ECHO is widely available and relatively inexpensive, views of the heart may be limited by obesity, small rib spaces and lung disease. The ability to differentiate adipose tissue from other tissues is also limited and operator dependent.

ECHO imaging studies have shown the mean EAT thickness at the right ventricular wall correlates significantly ($r = 0.840$, $P = 0.01$) with volume measurements using CMR [16]. Unfortunately, EAT thickness is only a surrogate marker for EAT volume, making it a sub-optimal imaging modality for prospective studies and clinical trials where absolute quantification of EAT volume is required. In addition, the low spatial resolution and operator dependency of ECHO makes delineating EAT from pericardial fat (or fluid) difficult, resulting in lower reproducibility compared to CT and MRI [17]. Unlike ECHO, cardiac CT can give excellent, reproducible 3D images and volume measurements that *can* be obtained without the use of intravenous contrast. However, these are costly and expose patients to ionizing radiation, although with the new faster scanners the dose is considerably reduced. Magnetic resonance imaging (MRI) is the gold standard for the assessment of total body fat and the reference modality for analysis of ventricular mass and volume [17], making it the natural choice for measuring EAT. CMR is expensive and even more limited in its availability, but does not expose the patient to radiation or IV contrast media. Even in general populations, CMR and EAT studies have been done in only small samples of patients. How representative these patients are of the general population is questionable and consequently defining reference values has proved problematic. A recent systematic review, however, concluded that EAT volumes of $>125\text{ml}$ or 68ml/m^2 , or EAT thickness $>5\text{mm}$ are abnormal

[17].

Epicardial adipose tissue measurement in haemodialysis patients

Several observational studies have looked at the thickness or volumes of EAT in HD patients compared to matched control groups. These are summarised in table 2. Altun *et al* were the first to demonstrate in an ECHO study of 62 HD patients and 40 healthy controls that EAT thickness was significantly larger in HD patients compared to controls (matched for age, sex, smoking status, BMI, cholesterol and triglyceride levels) and correlated positively with HD vintage [18**]. A further ECHO study by Atakan *et al* of 71 HD patients to 65 controls corroborated these findings, with controls in this study additionally matched for glucose levels [19**]. The first multi-directional CT (MDCT) study of EAT in HD patients was undertaken by Tonbul *et al*, who demonstrated EAT volume was significantly larger in diabetic patients on HD than in both healthy controls and patients on HD without diabetes [20], suggesting diabetic status may be the overriding driver behind EAT enlargement. However, a subsequent study using unenhanced coronary CT, by Turkmen *et al* found that EAT volumes were significantly higher in patients with ESRD on dialysis compared to matched controls independent of diabetic status. In the same study, although EAT volumes tended to be higher in patients on peritoneal dialysis (PD) compared to HD, this did not reach statistical significance [21].

A recent ECHO study by Colak *et al* showed that EAT thickness was significantly greater in patients on HD compared to patients who had a renal transplant (matched for BMI, body surface area, glucose, cholesterol, triglycerides, age and sex) but who were of a similar dialysis vintage prior to transplantation [22**]. The EAT thickness in the renal transplant group in this study was also similar to age and gender matched controls which may suggest there is something about the pro-inflammatory state of HD particularly that increases EAT thickness over and above the uraemic and inflammatory milieu associated with CKD alone.

All of these studies are observational and relatively small in size, nevertheless the data available suggests that EAT volumes are larger in HD patients compared

to controls. There are currently no CMR studies that have assessed EAT in HD patients

Epicardial adipose tissue and cardiovascular disease risk factors in haemodialysis patients

HD patients display hugely elevated rates of cardiac mortality [24], accounting for 43% of all cause deaths in this group [25]. Although the prevalence of traditional risk factors of CVD is higher in HD patients the increased rates of CVD are largely driven by non-traditional risk factors [26]. Several studies have reported significant associations between markers of CVD and EAT in HD patients. These are summarised in table 3. A cross-sectional study by Erdur *et al* showed that EAT volume (measured by MDCT) and atherogenic index of plasma (AIP), a logarithmic ratio of triglycerides to high density lipoprotein (HDL), were significantly higher in patients with ESRD on HD and PD than in healthy controls [23]. In addition there were significant correlations between EAT, BMI and AIP, with no correlation between EAT and AIP in healthy controls. An interventional pilot study by Wilund *et al* [27] showed that intra-dialytic exercise not only significantly reduced EAT thickness but also serum lipid peroxidation (a marker of oxidative stress), suggesting a relationship between the two. This is the only interventional study looking at the effects of exercise on EAT in HD patients. Gaus *et al* demonstrated in an observational study that EAT thickness measured using ECHO correlated well with BMI, smoking and age [28], and in a study of 191 prevalent HD patients, Turan *et al* found that EAT volume (assessed by MDCT) correlated significantly with older age, female gender, BMI, higher total cholesterol and triglyceride content, and in adjusted models, older age, BMI and total cholesterol continued to associate with increased EAT volume [29]. An echocardiographic study by Colak *et al* demonstrated that inflammatory markers (including CRP and Il-6) and cardiac volume indices (including left atrium index, left atrium diameter and inferior vena cava-collapse index) were significantly raised in HD patients and correlated significantly with EAT thickness when compared to both renal transplant and control patients. No such association was found between EAT thickness and these markers in the transplant patients [22**].

Turkmen [21], found significant relationships between EAT volume (assessed with MDCT) and increasing components of the malnutrition, inflammation and

atherosclerosis/calcification (MIAC) syndrome. The MIAC syndrome is defined as the interaction between pro-inflammatory cytokines, malnutrition and atherosclerosis in ESRD [30,31], which has been shown to be strongly associated with exceptionally high cardiovascular morbidity and mortality in patients with ESRD [32]. The same study by Turkmen *et al* also confirmed that increased volumes of EAT correlated positively with increasing age and BMI. It should be noted that the study population included patients with ESRD on HD and PD.

Epicardial adipose tissue and coronary artery disease in haemodialysis patients

EAT has been strongly associated with both the existence and severity of coronary artery disease (CAD) [33-35]; even patients with asymptomatic CAD have been found to have increased EAT volumes [36]. A meta-analysis in 2012 of 2872 patients with CAD concluded that on the available evidence EAT is an effective biomarker for the prediction of CAD [35].

The body of evidence for HD patients is somewhat smaller, but there are good observational data available. Atakan *et al* found with an echocardiographic study that EAT thickness correlated inversely with coronary flow reserve (CFR) in HD patients [19**]. CFR is a measure of how much coronary blood flow can increase and in the absence of epicardial disease reflects microvascular function. CFR has been used as a method for detecting endothelial dysfunction (ED) in non-renal populations and subsequent subclinical atherosclerotic CAD [37-39]. ED has also been shown to be a non-traditional risk factor for CAD and CVD morbidity and mortality in patients with ESRD [40,41]. Although the study by Atakan *et al* [19] is observational it demonstrates a clear association between EAT and ED and suggests the need for studies to look at causality.

Coronary artery calcification (CAC) is part of an extended state of vascular calcification that is detectable early in patients with ESRD and thought to contribute to both premature CVD and increased mortality [42]. The evidence for an association between EAT and CAC, is conflicting. In an observational study of 93 HD patients EAT assessed by echocardiography did not correlate with (CAC) except in younger patients [28]. However, an MDCT study of 60 HD patients and 20 matched controls found CAC to be associated with EAT volume in both diabetic patients and non-diabetic patients with ESRD [20]. Similarly, Turkmen *et al* found CACS and EAT volumes measured by CT were significantly higher in ESRD patients on HD and PD compared to healthy subjects and that there was a statistically significant relationship between EAT and CACS in all ESRD patients [21]. Further prospective studies are required to assess this relationship.

D'Marco *et al* [43] demonstrated through post-hoc analysis of the RIND trial [44] that EAT volume was an independent predictor of mortality in incident HD patients with a follow up period of around four years. Multivariate analysis demonstrated that for each 10cc increase in EAT volume there was a 6% increase in risk of death during follow-up. This is the first study to describe a significant association between EAT and mortality in HD patients, and corroborates the previously shown association of EAT with markers of vasculopathy such as CAC.

Clinical applications of epicardial adipose tissue in haemodialysis patients

EAT measurement has the potential to add value to CVD risk stratification in patients with ESRD. In non-renal groups EAT has been shown to be a good predictor of CAD [35]. In CKD patients not on dialysis, Cordeiro *et al* showed that EAT accumulation predicted the likelihood of cardiovascular events independently of general adiposity [15*]. Similarly, a cross-sectional study of non-diabetic HD patients by Ulsal Okyay *et al* [45*] demonstrated a robust association between EAT thickness, body fat accumulation, LV hypertrophy, dyslipidaemia, insulin resistance and delivered dialysis dose. Further prospective studies are required to confirm whether there is any added value to current CVD screening tools from EAT measurement in HD patients.

An interesting study by Karohl *et al* looked at the use of hybrid myocardial imaging for risk stratification prior to kidney transplantation [46]. This was a retrospective study of 411 patients with CKD 4-5D, 284 of which were on HD. The study used positron emission tomography (PET-CT) or single photon emission computed tomography (SPECT-CT) to assess myocardial perfusion and quantify CAC and EAT. Myocardial perfusion defects were present in only 10% of all patients evaluated, and on multivariate logistic regression EAT and CAC were independent predictors of abnormal myocardial perfusion, whilst presence of diabetes showed only a borderline association with the stress test result ($p=0.08$). EAT added incrementally to CAC for the prediction of an abnormal myocardial perfusion stress test, in a model including age, CAC, and diabetes mellitus (AUC 0.73 (95% CI 0.64-0.81) to 0.76 (95% CI 0.68-0.84, $p=0.02$) and was the best single predictor of abnormal myocardial perfusion. Although a retrospective study, this does suggest that EAT measurement may add some benefit to predicting myocardial perfusion defects in patients undergoing assessment for renal transplant. Further prospective studies are required and it should be noted that not all patients in this study had selective angiography, so confirmatory studies that include selective angiography are needed.

Two studies have shown EAT is potentially modifiable in HD patients. Wilund *et al* [27] showed EAT thickness could be reduced with a programme of

intradialytic exercise and Colak *et al* [22**] showed EAT thickness was significantly reduced in renal transplant patients who had previously been on HD compared to well-matched patients who were still on HD. Interventional studies that specifically target EAT reduction are needed, with mortality and cardiovascular events as end-points. Additionally, prospective studies that define the relationships between EAT and other risk factors, including silent and overt CAD, are required.

Conclusions

EAT is a metabolically active tissue which is increased in volume in dialysis patients and likely has a role in the pathogenesis of CVD in HD patients. We predict that EAT will have a role in the stratification of CV risk for dialysis patients and those considered for renal transplantation. This is not only because it is a predictor of mortality in HD patients but also because it improves sensitivity for predicting CV events. Finally, EAT is modifiable and may well be an attractive target for future interventional randomised controlled trials.

Key points

- EAT is likely to play a key role in the pathogenesis of CVD and CAD in HD patients through direct paracrine and vasocrine secretion of pro-inflammatory and pro-atherogenic cytokines into the myocardium.
- EAT measurement is likely to have a role in cardiovascular and cardiometabolic risk stratification for HD patients.
- EAT has been shown to be modifiable and as it potentially drives LVH, myocardial inflammation, endothelial dysfunction and coronary artery calcification it is an attractive therapeutic target.

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**of outstanding interest

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Table 1: Strengths and weaknesses of the imaging modalities commonly used to measure epicardial adipose tissue

	Trans Thoracic Echocardiography	Cardiac Computerized Axial Tomography	Cardiac Magnetic Resonance Imaging
Strengths	<ul style="list-style-type: none"> • Low cost • Widely available • No radiation 	<ul style="list-style-type: none"> • Total EAT volume measured • Highly reproducible • Simultaneous CAC assessment 	<ul style="list-style-type: none"> • Total EAT volume measured • Excellent tissue characterization • No radiation or IV contrast
Weaknesses	<ul style="list-style-type: none"> • Operator dependent • Limited acoustic windows • Low spatial resolution • Tissue characterization limited • Two dimensional 	<ul style="list-style-type: none"> • Expensive • Radiation exposure • Not widely available • May require intravenous contrast 	<ul style="list-style-type: none"> • Expensive • Time consuming • Certain contraindications to scanning • Expertise required in image acquisition and interpretation

EAT, epicardial adipose tissue; IV, intravenous; CAC, coronary artery calcification

Table 2: Studies comparing EAT volumes and thickness in HD patients with matched controls. Numbers of patients in each study group are given with control numbers in parentheses. Similarly, EAT measurements are given for each group with control values in parentheses. HD, haemodialysis; EAT, epicardial adipose tissue; ECHO, echocardiography; MDCT, multi-detector computerised tomography; ESRD, end stage renal disease.

Author	Year	Patient Groups	Number of patients	Imaging Modality Used	EAT Thickness or Volume
Altun [18**]	2014	HD patients	62 (40)	ECHO	6.98±1.67mm (3.84±0.73mm) p<0.001
Atakan [19**]	2014	HD patients	71 (65)	ECHO	6.53±1.01mm (5.79±1.06mm) p<0.001
Tonbul <i>et al</i> [20]	2011	HD patients with diabetes; HD patients without diabetes	17, 43 (20)	MDCT	215.5±126.5-271.2cm ³ ; 116.0±91.6-139.4cm ³ (104.0±87-134cm ³) p<0.001
Turkmen [21]	2011	ESRD patients	80 (27)	MDCT	160±76cm ³ (121.5±37.5cm ³) p=0.02
Colak [22**]	2015	HD patients; Renal transplant recipients	43, 45 (36)	ECHO	8.8±2.0mm; 5.6±1.4mm (5.0±0.3mm) p<0.001)
Erdur [23]	2013	ESRD patients	76 (42)	MDCT	160±76cm ³ (104±48cm ³)

Table 3: Associations between EAT in HD patients and markers of cardiovascular disease and/or metabolic dysfunction. Number of patients in each study group are given with control numbers in parentheses. EAT, epicardial adipose tissue; HD, haemodialysis; PD, peritoneal dialysis; AIP, atherogenic index of plasma; BMI, body mass index; CIMT, carotid intimal media thickness; MDCT, multi-dimensional computed tomography; CACS, coronary artery calcification score; ESRD, end stage renal disease; MIAC, malnutrition inflammation atherosclerosis calcification syndrome; Hs-CRP, highly sensitive C-reactive protein; IL-6, interleukin-6; HOMA-IR, homeostasis model assessment for insulin resistance; spKt/V, hemodialysis dose by single-pool urea clearance index.

Author	Year	Patient Groups	Number of patients	Imaging Modality	Significant Associations with EAT and risk marker
Erdur <i>et al</i> [23]	2013	ESRD patients	76 (42)	MDCT	EAT volume and AIP were significantly higher in patients with ESRD on HD and PD than in healthy controls, with significant correlations between EAT, BMI and AIP ($r=0.42$, $p<0.001$ and $r=0.25$, $p=0.028$, respectively). No correlation between EAT and AIP in healthy controls ($r=0.19$, $p=0.21$)
Gaus <i>et al</i> [28]	2014	HD patients	93	MDCT	EAT volume was found to correlate significantly with BMI and age. It also correlated with CACS in patients under 55 years of age.
Turan <i>et al</i> [29]	2013	HD patients	191	MDCT	EAT was found to correlate positively with carotid artery intima-media thickness ($r=0.229$, $p=0.001$), presence of carotid plaque ($r = 0.152$, $p = 0.03$) and pulse wave velocity ($r = 0.220$, $p = 0.002$). EAT volume was not different between patients with and without diabetes (61.9 ± 26.9 versus 66.5 ± 26.2 cm ³ /m ² , respectively, $p = 0.31$). Age, BMI and total cholesterol were independent predictors of EAT on adjusted analysis ($r=0.29$, $p=0.003$, $r=0.21$, $p=0.01$ and $r=0.24$, $p=0.01$ respectively)
Colak <i>et al</i> [22**]	2015	HD patients; Renal transplant recipients	43, 45 (36)	ECHO	EAT thickness significantly higher in HD patients than transplant patients of similar dialysis vintage prior to transplant and than to matched controls. In HD patients, EAT was positively correlated with age ($r=0.329$, $p=0.038$), BMI ($r=0.438$, $p=0.002$), dialysis vintage ($r=0.339$, $p=0.032$), Hs-CRP ($r=0.486$, $p=0.001$), IL-6

					($r=0.465$, $p=0.002$), left atrial index ($r=0.402$, $p=0.010$) and left ventricular mass index ($r=0.329$, $p=0.39$), and inversely correlated with inferior vena cava collapse index ($r=-0.460$, $p=0.003$).
Turkmen <i>et al</i> [21]	2011	ESRD patients	80 (27)	MDCT	Positive correlation between EAT and CACS in all ESRD patients ($r=0.48$, $p<0.001$). EAT increased significantly as number of MIAC components increased.
Altun <i>et al</i> [18**]	2014	HD patients	62 (40)	ECHO	EAT correlated positively with HD duration ($r=0.592$) and with CIMT ($r=0.7$). On multivariate regression, age, HD duration and CIMT were independent predictors of EAT
Atakan <i>et al</i> [19**]	2014	HD patients	71 (65)	ECHO	Coronary flow reserve was significantly reduced in HD patients ($p<0.001$) and correlated inversely with EAT thickness ($r=-0.287$, $p=0.02$)
Tonbul <i>et al</i> [20]	2011	HD patients with diabetes; HD patients without diabetes	17, 43 (20)	MDCT	EAT volumes significantly higher in HD patients with diabetes compared to HD patients without diabetes. Positive correlation between EAT and CACS in all ESRD patients ($r=0.48$, $p<0.001$)
D'Marco <i>et al</i> [43]	2013	HD patients	95	MDCT	Demonstrated that a 10 cc increase in EAT volume was associated with a significant 6% increase in the risk of death during follow-up [hazard ratio: 1.060; 95% CI: 1.013-1.109; P-value = 0.012]. EAT also correlated positively with age, BMI, triglycerides, CRP, CACS and aortic calcium, and negatively correlated with systolic and diastolic blood pressure, serum high density lipoprotein (HPL) cholesterol and serum phosphate (all $p<0.05$)
Ulusl Okyay <i>et al</i> [45*]	2015	HD patients	50	ECHO	EAT thickness showed significant associations with BMI ($\beta = 0.590$, $P < 0.001$), waist circumference ($\beta = 0.572$, $P < 0.001$), body fat mass ($\beta = 0.562$, $P < 0.001$), percentage of body fat mass ($\beta = 0.408$, $P = 0.003$), percentage of lean tissue mass ($\beta = -0.421$, $P = 0.002$), LV mass ($\beta = 0.426$, $P = 0.002$), CIMT ($\beta = 0.289$, $P = 0.042$), triglyceride/high-density lipoprotein cholesterol ratio ($\beta = 0.529$,

					P < 0.001), 1/HOMA-IR (β = -0.386, P = 0.006), and spKt/V (β = -0.311, P = 0.028)
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