

Correlation Between Epicardial Fat Thickness and Cardiovascular Risk in Hemodialysis Patients

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Abstract: *Background:* Cardiovascular diseases are common in hemodialysis (HD) patients and cardiovascular mortality is responsible for 50% of overall deaths in these patients. Epicardial fat thickness (EpFT) may be an effective marker for the prediction of cardiovascular diseases in hemodialysis patients. The thickness of EpF can be measured by echocardiography that can accurately estimate the actual amount of EpF. *The aim* of the current study is to assess the association between EpFT and carotid intima-media thickness (CIMT), left ventricular systolic and diastolic function and left ventricular mass index in patients with chronic kidney disease (CKD) undergoing hemodialysis to clarify the relationships between EpF and cardiovascular disease risk in these patients. *Materials and Methods:* Forty adult uremic patients from dialysis unit and twenty (age and sex matched) healthy control subjects were included in this study. Clinical evaluation, routine laboratory investigations, echocardiographic study including measurement of EpFT and carotid Duplex to estimate CIMT were done to all subjects. *Results:* we found highly significant increase in serum C-reactive protein and significant increase in serum phosphorus and triglyceride with significant decrease in serum calcium and high-density lipoprotein cholesterol in hemodialysis patients compared to the controls. Also, there were significant increases in left ventricular mass index, left atrium diameter, carotid intima-media thickness, epicardial fat thickness, peak velocity of the late filling wave due to atrial contraction (A wave) and deceleration time of E wave in hemodialysis patients compared to the controls. There were also highly significant decrease in E/A ratio in hemodialysis patients compared to healthy control subjects. EpFT measured by echocardiography in hemodialysis patients was positively correlated with body mass index, CRP, left atrium diameter, left ventricular mass index, deceleration time and CIMT and negatively correlated with high-density lipoprotein cholesterol and E/A ratio. *Conclusion:* Hemodialysis patients can be evaluated routinely by echocardiography for early detection of cardiovascular structural and functional changes which are common in these patients and epicardial fat thickness is an effective marker for the prediction of cardiovascular risk in hemodialysis patients.

Keywords: Hemodialysis Patients, Cardiovascular Diseases, Carotid Intima-Media Thickness, Epicardial Fat Thickness

1. Introduction

Chronic kidney disease (CKD) is highly prevalent affecting roughly 7% of the general adult population and up to one in three elder individuals [1]. Indeed cardiovascular mortality is responsible for 50% of overall deaths and is up to 20 times more incident in CKD individuals than in the general population [2]. Coronary artery calcification (CAC), a marker of subclinical vascular disease that is highly

prevalent in CKD, reliably predicts the risk for overall mortality and cardiovascular events in dialytic [3, 4] as well as in non-dialytic patients [5, 6].

Decreased glomerular filtration rate (GFR) and proteinuria were both found to be independently associated with coronary artery disease (CAD) [7-9]. The risk for CAD increases gradually with the decline of glomerular filtration

rates; that means that end-stage renal failure (ESRF) patients have the highest CVD risk among CKD population [10–13].

Atherosclerosis is a condition characterized with formation of plaques on the intimal layer of the vessels. Coronary atherosclerotic plaques constitute most of the vascular diseases in general population [14]. However, the pathophysiology of vascular disease in CKD is quite different from that related to atherosclerosis, in the general population [15]. Beside traditional risk factors including hypertension, diabetes, dyslipidemia, and advanced age, novel risk factors such as endothelial dysfunction, CKD abnormalities (hyperphosphatemia, hyperparathyroidism, and vascular calcifications), increased oxidative stress, and inflammation are highly prevalent and seem to play a more important role for vascular disease in CKD and ESRF patients compared to healthy subjects [16-19].

The spectrum of cardiovascular disease in CKD not only involves coronary artery disease, but also involves other disease states such as chronic heart failure, sudden death, and arrhythmias [20].

Left ventricular diastolic disease (LVDD) would be expected more frequently among patients with end stage renal disease (ESRD) than in the general population due to the inflammation, fluid overload, hypertension, renin-angiotensin-aldosterone system activation, and LV hypertrophy associated with ESRD [21& 22]. Abnormal fat distribution seems a likely culprit for the high prevalence of LVDD in patients undergoing dialysis. Such patients tend to have higher amounts of visceral adipose tissue associated with low-grade inflammation, which leads in turn to subclinical LVDD [23]. Epicardial fat (EpF) is characterized by a high rate of release of free fatty acids (FFA) [24], which encounter no physical barrier or fascia before reaching the cardiomyocytes [25]; therefore, the myocardium receives a double dose of FFA from both the EpF and the systemic circulation.

Visceral adipose tissue is highly metabolically active and produces hormones and cytokines, including those with anti-atherosclerotic properties (e.g. adiponectin [26]) and those with pro-atherosclerotic properties (e.g. Interleukin-6 (IL-6) and tumor necrosis factor α) [27]. Epicardial fat, a visceral deposit of adipose tissue located between the myocardium and visceral pericardium, is also metabolically active and produces many of the same pro-atherogenic cytokines found in visceral abdominal fat [25&28]. In patients with end stage kidney disease requiring dialysis, the total volume of epicardial fat is correlated with CAD [29], and is significantly greater in dialysis patients versus healthy controls [30].

Epicardial fat thickness (EpFT) is strongly associated with increased left ventricular mass (LVM) [31] documented by both autopsy and echocardiography [32&33]. Iacobellis *et al.* reported that this association was independent of systolic and diastolic blood pressure [33].

Epicardial fat can be assessed with computed tomography (CT), magnetic resonance imaging (MRI) and echocardiography. While CT and MRI have better image

quality than echocardiography and can be used to perform volumetric measurements, the high costs, low accessibility and complexity of measurement are major disadvantages. Echocardiography is the most preferred imaging method used to evaluate patients with palpitation in daily clinical practice, and it can also be used to easily measure EFT with high reproducibility [34& 35].

Carotid intima-media thickness (CIMT) is a surrogate marker for atherosclerosis and can be used to detect an accelerated disease process and subclinical disease [36]. Carotid intima-media thickness is greater in hemodialysis patients compared to the control group [37]. CIMT remained a consistent predictor of fatal cardiovascular events indicates that this measurement bears a prognostic value on the dialysis population; a 0.1-mm increase in CIMT predicts a 24% higher risk for cardiovascular death [38&39].

Carotid intima-media thickness (CIMT) is a potential indicator of subclinical atherosclerosis. Epicardial fat thickness (EpFT) is suggested as a new cardio metabolic risk factor. EpFT is associated with increased CIMT [40].

Atakan *et al.*, found that epicardial fat thickness was significantly higher among HD patients compared to healthy controls. In addition, their study was the first to demonstrate an inverse correlation between EpFT and coronary flow reserve in these patients [41].

Turan *et al.*, reported that EpFT was associated with carotid intima-media thickness, arterial stiffness and coronary artery calcification [42]. Also Turkmen *et al.*, showed an association between EpFT volume and coronary artery calcification in dialysis patients [43].

2. Aim of the Study

The aim of our current study is to assess the association between EpFT, carotid intima-media thickness and left ventricular systolic and diastolic function and left ventricular mass index in patients with CKD undergoing hemodialysis to clarify the relationships between EpF and cardiovascular disease risk in these patients.

3. Subjects and Methods

Forty adult uremic patients from dialysis unit of Theodor Bilharz Research Institute were included in this study. All patients were treated by conventional hemodialysis, 3 sessions weekly, 4 hours each.

Patients with clinical signs of heart failure, atrial fibrillation, uncontrolled hypertension, liver diseases, severely anemic patients with Hb <10g/dl and patients with malignancy or active inflammation were excluded from the study.

Twenty (age and sex matched) healthy control subjects, selected from medical and paramedical staff were included in this study.

All patients were provided by informed consent, and the ethical committee of hospital approved this study.

All patients and controls in this study were subjected to the

following:

--Full clinical examination.

--Laboratory investigation: blood samples were collected from all patients from the antecubital vein between 8:00 AM and 10:00 AM with the patient in a supine position after fasting for 12 hr. Plasma glucose, complete blood picture, liver functions (AST, ALT, and albumin), renal functions (urea and creatinine), serum total calcium, serum phosphorus, serum electrolytes (sodium and potassium), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), and C-reactive protein (CRP) levels were determined.

--Electrocardiogram (ECG): resting 12-lead surface electrocardiogram was carried out to detect evidence of left ventricular hypertrophy, ischemic heart disease, pericarditis or pericardial effusion.

--Echocardiography: left atrial (LA) diameter, the LV end-diastolic and systolic diameters, interventricular septum thickness, LV posterior wall thickness, mitral inflow early rapid filling wave (E) velocity, peak velocity of the late filling wave due to atrial contraction (A), E/A ratio and E wave deceleration time were measured according to the American Society of Echocardiography guidelines using a high resolution (ALT 5000 HDI) Toshiba Nemo 30 scanner equipped with a 2.5 MHz transducer [44]. The LV mass index was calculated from the LV end-diastolic diameter, interventricular septum thickness, and LV posterior wall thickness according to the method of Devereux et al. $LVM\text{ gm} = 1.04 \times \{(LVEDD + IVST + PWT)^3 - LVEDD^3\} \times 0.8 + 0.6$ [45]. Doppler and color Doppler studies were performed to detect valvular heart disease [44].

--Epicardial fat thickness was identified as the echocardiographically free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured perpendicularly to the free wall of the right ventricle at end-systole over 3 cardiac cycles. The mean value of 3 cardiac cycles from each echocardiographic view (including both parasternal long- and short-axis views) was recorded as the EpF thickness [46].

--Carotid Duplex: high resolution B mode ultrasonography of both the common carotid arteries were performed using an ultrasound machine (Toshiba Nemo 30 scanner) equipped with a 7.5 MHz high resolution transducer. CIMT was defined as a low-level echo gray band that does not project into the arterial lumen [47] and was measured during end-diastole as the distance from the leading edge of the second echogenic line of the far walls of the distal segment of the common carotid artery, the carotid bifurcation, and the initial tract of internal carotid artery on both sides.

4. Statistical Analysis

Statistical analysis was performed using SPSS version 17. Data were expressed as the mean \pm standard deviation (SD) for numerical variables. $P \leq 0.05$ was considered to be statistically significant and $P < 0.01$ was considered to be highly statistically significant.

5. Results

Forty adult uremic patients from dialysis unit of Theodor Bilharz Research Institute, (16 females and 24 males), were treated by conventional hemodialysis, 3 sessions weekly, 4 hours each and twenty (age and sex matched) healthy control subjects, selected from medical and paramedical staff were included in this study.

Demographic features of hemodialysis patients and healthy control subjects were demonstrated in (table1). There were highly significant increase in systolic and diastolic blood pressure and in percent of diabetes mellitus in hemodialysis patients compared to healthy control subjects.

There were highly significant increase in serum creatinine, urea and C-reactive protein and there were also significant increase in serum phosphorus and triglyceride in hemodialysis patients compared to healthy control subjects. There were also highly significant decrease in estimated glomerular filtration rate, serum calcium and high-density lipoprotein cholesterol in hemodialysis patients compared to healthy control subjects (table2).

Table 1. Demographic features of hemodialysis patients and healthy control subjects:

	Dialysis Patients (n=40)	Control (n=20)	Sig.
Age (Yrs)			
Range	23-75	25-70	
Mean \pm SD	56.07 \pm 11.87	51.55 \pm 13.42	NS
Sex			
Male	24(60%)	11(55%)	NS
Female	16(40%)	9(45%)	NS
Weight(Kg)	73.67 \pm 14.54	79.35 \pm 13.87	NS
BMI(Kg/m ²)	25.58 \pm 5.0	27.6 \pm 4.19	NS
Systolic blood Pressure(mmHg)	136.5 \pm 16.4	112.1 \pm 7.6	HS
Diastolic blood Pressure(mmHg)	78.8 \pm 6.2	69.2 \pm 3.8	HS
DM(%)	75%	--	HS
DOD(Yrs)	3.27 \pm 4.5	--	

BMI, Body mass index; DOD, Duration of dialysis; DM, Diabetes Mellitus; NS, Non Significant; HS, Highly Significant ($P < 0.01$).

Table 2. Biochemical Laboratory data of hemodialysis patients and healthy control subjects:

	Dialysis Group (n=40)	Control Group (n=20)	P(value)	Sig.
S.Creatinine(mg/dl)	7.815 \pm 2.783	0.815 \pm 0.253	<0.01	HS
Urea(mg/dl)	113.85 \pm 34.542	26.75 \pm 3.316	<0.01	HS
eGFR	5.0 \pm 1.1	98.8 \pm 25.87	<0.01	HS
S.Calcium(mg/dl)	7.98 \pm 1.14	9.13 \pm 0.675	<0.01	HS
S.Sodium(mEq/l)	135.1 \pm 2.75	134.83 \pm 2.75		NS

	Dialysis Group (n=40)	Control Group (n=20)	P(value)	Sig.
S.Potassium(mEq/l)	4.568±0.690	4.35±0.370		NS
S.Phosphorus(mg/dl)	4.82±1.53	3.615±0.64	0.02	S
S.Cholesterol(mg/dl)	189.46±48.15	187.9±20.39	0.439	NS
Triglyceride(mg/dl)	141.6±65.21	102.8±19.63	0.02	S
HDL(mg/dl)	35.15±6.057	42.95±3.167	<0.01	HS
LDL(mg/dl)	122.246±44.37	120.55±23.10	0.378	NS
CRP(mg/l)	7.3±2.6	1.7±0.4	<0.01	HS

eGFR, Estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and CRP, C-reactive protein. HS, Highly significant; S, Significant; NS, Non significant

There were highly significant increase in posterior wall thickness, interventricular septum thickness, left ventricular mass, left ventricular mass index, left atrial diameter, carotid intima-media thickness and epicardial fat thickness and also there were significant increase in peak velocity of the late filling wave due to atrial contraction and deceleration time in hemodialysis patients compared to healthy control subjects. There were also highly significant decreased E/A ratio in hemodialysis patients compared to healthy control subjects (table3).

Table 3. Echocardiographic data of hemodialysis patients and healthy control subjects:

	Dialysis Patients (n=40)	Control Group (n=20)	P(value)	Sig.
EF(%)	63.833±8.93	68.86±3.31	0.13	NS
FS(%)	34.98±6.549	38.66±3.45	0.3	NS
LVEDD(mm)	52.92±7.88	47.93±6.57	0.52	NS
LVESD(mm)	34.85±8.29	32.37±5.58	0.483	NS
PWT(mm)	11.11±2.22	8.7±1.06	<0.01	HS
IVST(mm)	11.24±2.43	8.68±0.97	<0.01	HS
LVM(gm)	241.27±80.43	142.35±42.43	<0.01	HS
LVMI	138.87±55.73	74.8±16.4	<0.01	HS
LA(mm)	38±6.5	35±5.3	<0.01	HS
E velocity(m/s)	0.58±0.26	0.60±0.15	0.104	NS
A velocity(m/s)	0.65±0.44	0.59±0.17	0.04	S
DT(ms)	198±67	189±56	0.014	S
E/A	0.9±0.4	1.1±0.5	<0.01	HS
CIMT(mm)	12.2±1.9	7.1±2.8	<0.01	HS
EpFT(mm)	5.41±1.81	4.07±1.34	<0.01	HS

EF, Ejection fraction; FS, Fraction shortening; LV EDD Left ventricular end-diastolic diameters; LVESD Left ventricular end-systolic diameters; PWT, posterior wall thickness; IVST, Interventricular septum thickness; LVM, Left ventricular mass; LVMI, Left ventricular mass index; LA, Left atrial diameter; E, mitral inflow early rapid filling wave velocity; A, peak velocity of the late filling wave due to atrial contraction; E/A ratio; DT, deceleration time; CIMT, Carotid intema-media thickness; and EpFT, Epicardial fat thickness. HS, Highly significant; S, Significant; NS, Non significant.

The variables correlated with EpFT in hemodialysis patients were age, body mass index, systolic and diastolic blood pressure, high-density lipoprotein cholesterol, CRP, left atrium diameter, left ventricular mass index, E/A ratio,

deceleration time and carotid artery intima-media thickness (table 4).

Table 4. The univariate correlations of the epicardial fat thickness.

Variable	R	P
Age	0.265	0.02
Body mass index	0.315	<0.01
Systolic blood pressure	0.368	<0.01
Diastolic blood pressure	0.372	<0.01
High-density lipoprotein cholesterol	-0.312	<0.01
C reactive protein	0.435	<0.01
Left atrium diameter	0.356	<0.01
Left ventricular mass index	0.354	<0.01
E/A ratio	-0.386	<0.01
Deceleration time	0.374	<0.01
Carotid artery intima-media thickness	0.479	<0.01

Significant; (P<0.05), Highly Significant (P<0.01).

Epicardial fat thickness in hemodialysis patients was significantly correlated positively with age, highly significantly correlated positively with body mass index, systolic and diastolic blood pressure, CRP, left atrium diameter, left ventricular mass index, deceleration time and carotid artery intima-media thickness and highly significantly correlated negatively with high-density lipoprotein cholesterol and E/A ratio.

6. Discussion

Traditional cardiovascular risk factors including diabetes, hypertension and dyslipidemia are common among hemodialysis patients. However the high prevalence of atherosclerosis and arterial calcification in hemodialysis patients is far beyond the explanation by common cardiovascular risk factors [48].

In our study, there were highly significant increase in systolic and diastolic blood pressure and in percent of diabetes mellitus in hemodialysis patients compared to healthy control subjects. Our study agrees with other studies which found that the prevalence of hypertension was 86% in hemodialysis patients and was 25% in general population [49& 50]. When ambulatory blood pressure monitoring was used to assess systolic hypertension in hemodialysis population the prevalence was 73% [49]. Also our study agrees with other studies that reported that DM occurs among patients receiving dialysis at rates greater than in the general population [51-53].

In our study, there were highly significant increase in

serum triglyceride and highly significant decrease in high-density lipoprotein cholesterol in hemodialysis patients compared to healthy control subjects. Our study agrees with other studies which found that the renal dyslipidemia is reflected in an abnormal apolipoprotein (apo) profile and in the concentrations and composition of individual lipoprotein families [54, 55]. It is characterized by reduced concentrations of apoA-containing lipoproteins in high-density lipoprotein (HDL) and increased concentrations of intact or partially metabolized triglyceride-rich apoB-containing lipoproteins in VLDL, intermediate-density lipoprotein (IDL), and LDL [55, 56]. There is a preferential increase in the levels of IDL and small dense LDL [57&58]. The principal features of renal dyslipidemia remain essentially unchanged during HD, but the expression of dyslipidemia can be moderately attenuated during long-term HD [59].

There is a strong association between chronic inflammation and dysregulation of calcium, phosphate, and the parathyroid hormone, which lead to coronary atherosclerosis, arterial calcification and cardiovascular complications in chronic hemodialysis patients [60, 61].

In the current study, there was a significant increase in serum phosphorus in patient group versus the control group. This is in agreement with the study done by Spasovski who stated that the abnormalities in bone and mineral metabolism in CKD patients regarding hypocalcemia and hyperphosphatemia are associated with an increased risk of fractures, vascular calcifications and cardiovascular disease (CVD) [62].

The inflammatory marker CRP exhibited highly significant elevation in hemodialysis patients versus the control group. In agreement with these results, Jeznach-Steinhagen et al., reported that there is evidence that hemodialysis patients are in a state of chronic inflammation with activation of C-reactive protein and proinflammatory cytokines and is associated with increased oxidative stress and endothelial dysfunction [63].

In the current study, the echocardiographic data showed a highly statistically significant increase in interventricular septum thickness at end diastole (IVST), posterior wall thickness at end diastole (PWT) and left ventricular mass index (LVMI) in hemodialysis patients compared to the controls ($P<0.01$). Our study agrees with the study of Resic and his colleague [29] who found increased left ventricular wall thickness in 55.8% of patients on chronic hemodialysis compared to the control group [64]. Our study agrees also with recent studies which found a highly statistically significant increase in IVST, PWT and LVMI in hemodialysis patients compared to the controls ($P<0.01$) [65,66].

The present study, revealed that carotid intima-media thickness (CIMT) was highly significantly increased in patients with chronic hemodialysis than the control group ($P<0.01$). Common carotid artery intima-media thickness, as a measure of coronary artery disease and subclinical vascular disease, was found to be increased in patients with chronic

hemodialysis than the control group [67]. Also our study agrees with recent studies which found a highly statistically significant increase in CIMT in hemodialysis patients compared to the controls ($P<0.01$) [65, 66].

Left ventricular diastolic heart failure would be expected more frequently among patients with end stage renal disease (ESRD) than in the general population due to the inflammation, fluid overload, hypertension, renin-angiotensin-aldosterone system activation, and LV hypertrophy associated with ESRD [21].

In the current study left ventricular diastolic function (E/A ratio and deceleration time) showed significantly higher dysfunction in the dialysis group compared to the control group. These results are similar to those reported by Gagliardi and his colleagues that also found 70% of their studied hemodialysis patients have diastolic dysfunction [68]. This finding also agrees with Fathi and his colleagues, who reported impaired left ventricular diastolic velocity in patients with ESRD [69]. Manes and his colleagues, in their study of Left ventricular geometric patterns and cardiac function in patients with chronic renal failure undergoing hemodialysis also found that diastolic dysfunction was found in 87% of patients. The relatively higher percentage in their study may be explained by their enrollment of diabetic patients in their study [70].

The present study, revealed that epicardial fat thickness was highly significantly increased in hemodialysis group than the control group ($P<0.01$). Our study agrees with a recent study which demonstrated that EFT was significantly higher among HD patients compared to healthy controls [41].

In our current study, we measured the thickness of EpF by echocardiography. Malavazos et al. documented that echocardiographic measurement accurately estimates the actual amount of EpF, which could be a strong and independent predictor of myocardial fat. Echocardiographic EpF measurement has advantages for use in both clinical and research settings, including low cost, routine applicability, avoidance of exposure to radiation, and potential for monitoring therapeutic effects [46].

In our study we found that Epicardial fat thickness in hemodialysis patients was significantly correlated positively with age, highly significant correlated positively with body mass index, systolic and diastolic blood pressure, CRP, left atrium diameter, left ventricular mass index, deceleration time and carotid artery intima-media thickness and highly significantly correlated negatively with high-density lipoprotein cholesterol and E/A ratio. Diastolic dysfunction was represented by E/A ratio and deceleration time.

This is in agreement with the recent study of Kocyigit and his colleagues that showed highly significant positive correlation between epicardial fat thickness and these parameters in dialysis patients; age, body mass index, systolic and diastolic blood pressure and CRP [71]. Also in another recent study EpFT measured from parasternal long and short-axis showed statistically significant positive correlation with age ($r=0.354$, $p<0.001$; $r=0.286$, $p<0.001$ respectively), and waist circumference ($r=0.189$, $p=0.019$;

$r=0.217$, $p=0.007$ respectively) and also significant negative correlation between EpFT from the parasternal long axis with cholesterol-HDL was observed ($r=-0.163$, $p=0.045$) [72]. Epicardial fat thickness in other study found to be positively correlated with age and BMI [30]. Other study using univariate analysis demonstrated the strongest associations between EpF volume and body mass index (BMI) ($r=0.53$; $P<0.0001$), abdominal obesity ($r=0.51$; $P<0.01$) and high density lipoprotein (HDL) cholesterol ($r=-0.39$; $P<0.01$) [73].

In our study we found that epicardial fat thickness in hemodialysis patients was correlated highly significantly with left atrium diameter and this is in agreement with the study of Iacobellis *et al.*, and that of Konishi *et al.*, who found that epicardial fat thickness was correlated highly significantly with left diameter ($P<0.01$) [74, 75].

Our study showed that epicardial fat thickness in hemodialysis patients was correlated highly significantly with left ventricular mass index. This is in agreement with Corradi *et al.* who thought that EpFT have an important role in left ventricular hypertrophy [32]. On the other hand, HDL had an independent negative relationship with LVM. HDL is a metabolic syndrome parameter and may represent it; therefore, absence of metabolic syndrome may be protective for increase in LVM [76-78].

In the current study, we found that EpF thickness in patients undergoing HD correlates with left ventricular diastolic dysfunction (LVDD). This is in agreement with the study of Van der Meer which showed that myocardial fat has progressive and harmful effects on LV diastolic function [79]. EpF is characterized by a high rate of release of free fatty acids (FFA) [24], which encounter no physical barrier or fascia before reaching the cardiomyocytes; [25] therefore, the myocardium receives a double dose of FFA from both the EpF and the systemic circulation. There are also hypothesis that EpF can influence LV diastolic function. EpF is a source of several bioactive molecules that might directly influence the myocardium [80]. In metabolic and cardiovascular disease states, these fat tissues expand, becoming hypoxic and dysfunctional [81,82] and recruiting phagocytic cells [83] which would lead to reducing the production of protective cytokines, increasing detrimental adipocytokines and impaired cardiac function eventually.

Our study revealed that EpF thickness in patients undergoing HD correlates with carotid intima-media thickness which agrees with a recently published study by Turan *et al.*, who concluded that EpF volume is correlated with cardiovascular surrogate markers such as carotid intima-media thickness and pulse-wave velocity [42]. In a study by Turkmen *et al.*, the authors found a significant relationship between EpF volume and the presence of the malnutrition-inflammation-atherosclerosis calcification syndrome in HD patients [30]. In another study by the same group, they reported a relationship between EpFT and coronary artery calcification among peritoneal dialysis patients [43]

A recent meta-analysis showed that EpFT may be an effective marker for the prediction of coronary heart disease

[84]. Epicardial fat thickness produces a large amount of cytokines and proinflammatory mediators such as tumor necrosis factor-alpha and interleukin-6, and it is believed to promote atherosclerosis via paracrine effects [85, 28]. The direct contact with the coronary arteries of an inflamed EpF may induce vasa vasorum proliferation that penetrate through the arterial wall toward the intima and promote atherosclerosis [86]. The proatherosclerotic activity of the EpF is indirectly suggested by its close association with vulnerable atherosclerotic plaques and the risk of incident cardiovascular event [87-90].

The mechanisms that promote the development of CAD through epicardial fat are not completely clear. The role of epicardial fat as a metabolically active organ with paracrine or endocrine functions is the most accepted. Previous studies have shown that adipose tissue, particularly visceral fat, express numerous genes related to adipokine production, which have important roles in the development of atherosclerosis in obese patients [28, 91]. Epicardial fat located near to the coronary tree could facilitate the paracrine effects of epicardial adipokines, as part of the pathogenesis of CAD [92&93].

7. Conclusion and Recommendation

Hemodialysis patients can be evaluated routinely by echocardiography for early detection of structural and functional cardiovascular abnormalities which are common in these patients and may lead to high morbidity and mortality.

Epicardial fat thickness in hemodialysis patients is correlated significantly with left atrium diameter, left ventricular mass index, diastolic dysfunction (E/A ratio, deceleration time) and carotid artery intima-media thickness (which is an indicator of atherosclerosis). So, epicardial fat thickness which can be easily measured by Echocardiography is an effective marker for the prediction of cardiovascular disease risk in hemodialysis patients.

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