Relation of Epicardial Fat and Diabetic Nephropathy in Egyptian Patients

Mohamed Abdel-Azeem Mohamed, Salwa Roshdy Dimitry,
Magdy Ibrahim Aldesowky M. Algowhary
Department of Cardiology, Faculty of Medicine, Assiut University, Assiut, Egypt.
Corresponding Author: Mohamed Abdel-Azeem Mohamed
E-mail: *dr.mon_85@hotmail.com*

Abstract:

Background*:* Visceral fat can be measured directly by epicardial fat thickness rather than anthropometric measurements. Two-dimensional (2D) echocardiography can accurately measure EFT. Our study pointed to detecting the role of EFT in predicting coronary artery disease (CAD), nephropathy, and affected vessels by 2D echocardiography.

Methods*:* A cross-sectional, prospective study enrolled 120 patients who underwent coronary angiography and correlated the relation between EFT, nephropathy, and CAD. Patients signed informed consent. This study was approved by the ethical committee of the Faculty of Medicine, Assiut University (IRB Number: 17100450).

Results*:* EFT was considered an independent risk factor for CAD (OR= 10.081, AUC= 0.936 with 86.5% accuracy at cut-off point > 0.55) and affected vessels (OR= 14.021, AUC= 0.981 with 87.5% accuracy at cut-off point > 0.45 cm) in diabetic patients. Also, we found that EFT was considered an independent risk factor for nephropathy (OR= 4.365, AUC= 0.601 with 72% accuracy at cut-off point > 0.45), CAD (OR= 18.635, AUC= 0.977 with 90.5% accuracy at cut-off point > 0.45) and affected vessels (OR= 8.826, AUC= 0.979 with 91.5% accuracy at cut-off point > 0.45 cm) in all studied patients.

Conclusions*:* EFT assessment is a simple, non-invasive tool for predicting nephropathy and CAD and their severity. In addition to the known cardiovascular risk factors, EFT may help identify the risk of cardiovascular disease. Multi-center future studies are warranted to confirm such results.

Keywords: Epicardial fat thickness, diabetic nephropathy, coronary artery disease.

Background

Diabetes mellitus (DM) is described as a clinical metabolic disorder with an increasing prevalence and incidence rate. Renal disease in diabetic patients is related to increased mortality and morbidity owing to their extremely high cardiovascular risk (1, 2).

Diabetic nephropathy (DN) is a known cause of mortality and morbidity in diabetic patients. DN is the primary cause of DM cases with CAD. Additionally, a poor prognosis for cardiovascular disease is indicated by elevated albuminuria and decreased renal function (3, 4).

With characteristics resembling visceral adipose tissue, epicardial fat is a biologically active organ linked to coronary artery disease and metabolic disorders. The EFT has an advantage over known cardiovascular risk factors, such as body mass index, coronary artery disease (CAD) onset, and DN in their early stages, which can be predicted accurately (5, 6).

EFT has also been suggested as a cardiovascular risk in both populations and patients with chronic kidney disease. It has also been shown that EFT is a highly active organ that produces bioactive adipokines, pro-inflammatory and pro-atherogenic cytokines (7).

EFT can be measured using 2D echocardiography, C- MRI, or cardiac CT (8). However, its importance in patients with diabetes and DN has not been thoroughly investigated. So, this research tried to assess the applicability of epicardial fat thickness (EFT) measurement by two-dimensional echocardiography to predict CAD and DN.

Methods

Study Setting& Design

A cross-sectional study was conducted at Assiut University Heart Hospital. The study was conducted between October 2020 and February 2022.

Ethical Approval

The study was done according to the rules of the Declaration of Helsinki and was approved by the Hospital's Ethics Committee. The purpose of the study was illustrated to all patients, and written informed consent was obtained. The study was registered on *clinicaltrials.gov* with NCT03470415.

Patients signed informed consent.

IRB: Assiut Faculty of Medicine approved the study.

IRB Number: 17100450

Participants and Sample Size

The sample size was calculated using G*power, version 3.1.9.2. Based on a previous study, the mean of EFT for normoalbuminuria patients was 4.98 mm, for macroalbuminuria patients was 4.97 mm, and for microalbuminuria patients was 6 mm (5). The calculated effect size was 0.319, with a power of 80% and α of 0.5; the sample needed for the study was estimated to be about 100 patients with an expected 10% dropout; 120 patients were enrolled.

Selection Criteria

Any diabetic patient and/or patient with renal complaints aged between 30 and 65 years were eligible for the study. Exclusion criteria included age < 30 or> 65 years, type 1 DM, cardiac disease (ischemic heart disease, congenital heart disease), active infection, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematous), acute diabetic complications, other causes of nephropathy (liver cirrhosis, drug-induced, end-stage renal disease on regular hemodialysis) and /or family history of CKD.

All participants were evaluated as follows:

Through history taking, which included demographic data such as age, sex, and comorbidities. A full clinical evaluation was done. The following investigations were performed: fasting blood glucose (FBG), glycosylated hemoglobin (HbA1C), kidney function tests, C-reactive protein, complete blood count, liver function tests, and urine analysis for albuminuria.

Calculation of "eGFR" by the Cockcroft-Gault equation ((140-age in years) * (weight in kg))/ (creatinine in mg*72)). The patient was instructed to fast overnight and avoid cooked meat before the test (9).

An electrocardiogram was done for all patients.

Abdominal ultrasound

To assess the echogenicity of the kidneys and other abdominal organs

Echocardiography

Transthoracic echocardiography of all patients uses an echocardiograph with a broadband transducer (Vivid 5). Images were recorded. A 2-D view identifies EFT as an echo-free space in the pericardial layers. EFT was computed on the free wall of the right ventricle at the end-diastole in parasternal long- and short-axis views. The average Measures from both were calculated.

Coronary Angiography

All patients underwent coronary angiography to assess coronary artery disease.

Statistical Analysis

Data was collected and analyzed using SPSS (Statistical Package for the Social Sciences, version 20, IBM, Armonk, New York). Quantitative data were expressed as mean and SD, while nominal data were given as number (n) and percentage (%).

Predictors of DN, CAD, and affected vessels in all patients or those with diabetes only were assessed by logistic regression analysis. The receiver operator characteristic curve was used to assess the diagnostic accuracy of osteopontin in predicting PFT in DN and CAD prediction. It affected vessels in all patients or in those who had diabetes only. The confidence level was kept at 95%; hence, the *P* value was considered significant if < 0.05.

Results

Characteristics of all enrolled patients (Table 1):

The mean age of enrolled patients was 57.55 (years); the majority (69.2%) of patients were males. Out of those patients, 101 (84.2%) were diabetics. EFT by echocardiography was 0.64 ± 0.20 (cm). There were 97 (80.8%) patients who had abnormal coronary angiography. Other characteristics are summarized in Table 1.

Predictors for Nephropathy (Table 2):

Each male sex, EFT, glycosylated hemoglobin, PLR, and diseased vessels were considered independent risk factors for nephropathy in all patients. With ROC analysis, at a cut-off point > 0.45 cm, EFT had 84% sensitivity, 60% specificity, and 72% accuracy, with AUC of 0.601 and *p*= 0.096 **(Figure 1A).**

Predictors for Coronary Artery Disease (Table 3):

Each EFT, glycosylated hemoglobin, GFR, NLR, abnormal ECG, and echo EF% is considered an independent risk factor for CAD in all patients. With ROC analysis, at a cut-off point > 0.45 cm, EFT had 100% sensitivity, 81% specificity, and 90.5% accuracy, with an AUC of 0.977 and $p < 0.001$**(Figure 1B).**

Predictors for Affected Vessel (Table 4):

Each EFT, age, duration of DM, glycosylated hemoglobin, positive family history, PLR, GFR, and abnormal ECG is considered an independent risk factor for affected vessels in diabetic patients. With ROC analysis, at a cut-off point > 0.45 cm, EFT had 100% sensitivity, 83% specificity, and 91.5% accuracy, with an AUC of 0.979 and $p < 0.001$ **(Figure 1C).**

Legend of Tables

Table 1: Characteristics of all enrolled patients

	N= 120
Age (years) Range	57.55 ± 8.20 36-76
Male	83 (69.2%)
Diabetes mellitus	101 (84.2%)
Duration of diabetes mellitus (years)	7.71 ± 5.30
Treatment of diabetes mellitus (n= 101) Insulin Oral hypoglycemic agents	 29 (28.7%) 72 (71.3%)
Smoking	51 (42.5%)
Family history of diabetes mellitus	11 (9.2%)
Hyperlipidemia	67 (55.8%)
Hypertension	65 (54.2%)

EFT (cm)	0.64 ± 0.20
Diseased vessels	97 (80.8%)
Abnormal electrocardiogram	97 (80.8%)
Ejection fraction (%)	60.81 ± 4.9
Wall motion abnormality	13 (10.8%)

Data is expressed as frequency (percentage), mean (SD), and range. EFT: epicardial fat thickness

Table 2: Predictors for diabetic nephropathy

Predictor	**OR (95% CI)**	***P-value***
Age/years	1.020 (0.864 – 1.203)	= 0.817
Sex (Male)	0.105 (0.018 – 0.615)	= 0.012
ECFT/cm	4.365 (1.899 – 8.014)	= 0.014
HbA1C	2.214 (1.067 – 5.069)	= 0.030
PLR	6.421 (1.320 – 18.233)	= 0.012
Diseased Vessel	11.857 (1.232 – 24.482)	= 0.032

*ECFT: Epicardial fat thickness *PLR : platelet _lymphocytic ratio

Table 3: Predictors for coronary artery disease

Predictor	**OR (95% CI)**	**P-value**
Age/years	1.699 (0.443 – 12.104)	= 0.125
Sex (Male)	0.564 (0.192 – 1.654)	= 0.298
ECFT/cm	18.365 (2.351 – 48.254)	= 0.001
HbA1C	9.089 (1.564 – 15.124)	= 0.023
NLR	4.021 (1.474 – 8.969)	= 0.007
GFR	0.950 (0.918 – 0.983)	= 0.042
Abnormal ECG	24.957 (4.241 – 58.901)	= 0.033
Echo EF%	0.555 (0.427 – 0.722)	= 0.007

*ECFT: Epicardial fat thickness *NLR : Neutrophil _lymphocytic ratio
*GFR: Glomerular filtration rate

Table 4: Predictors for affected vessel

Predictor	**OR (95% CI)**	***P-value***
Age/years	1.080 (1.021 – 1.143)	= 0.008
Sex (Male)	0.594 (0.192 – 1.657)	= 0.298
ECFT/cm	8.826 (1.599 – 14.081)	= 0.001
Duration of DM/years	3.045 (1.155 – 8.018)	= 0.024
HbA1C	4.341 (1.088 – 9.817)	= 0.022
Positive Family History	4.213 (1.160 – 15.305)	= 0.029
PLR	3.928 (1.299 – 11.882)	= 0.015
e-GFR	0.950 (0.918 – 0.983)	= 0.003
ECG Abnormality	12.102 (4.532 – 22.114)	= 0.025

*ECFT: Epicardial fat thickness *PLR : platelet _lymphocytic ratio *e-GFR:estimated Glomerular filtration rate

Legend of Figure

FIG 1A , 1B , 1C

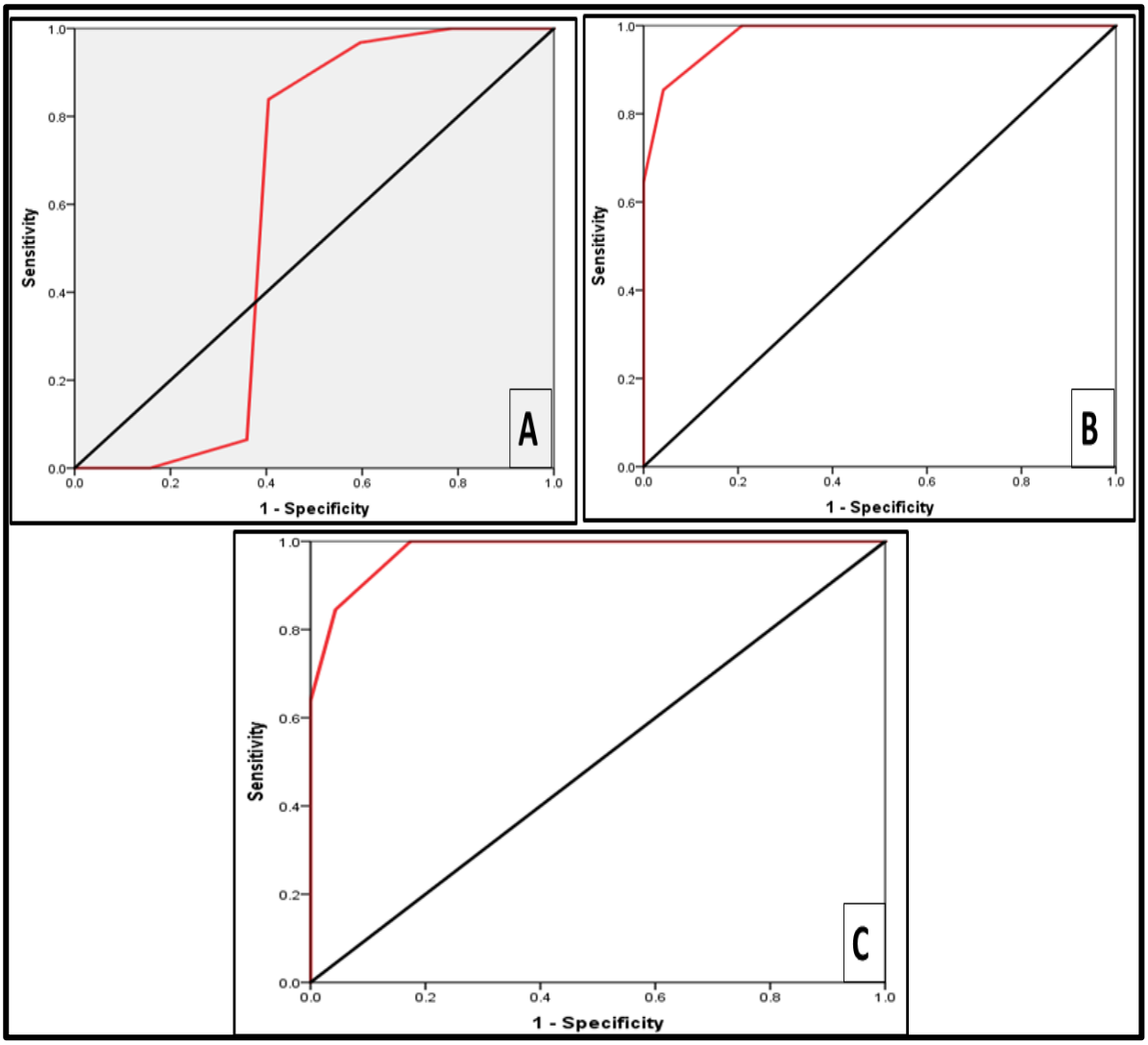

Figure 1: ROC curve for EFT for the prediction of
(A) Nephropathy at cut-off point > 0.45cm (B) CAD at cut-off point > 0.45cm, and
(C) Affected Vessels at cut-off point > 0.45 cm
"in the Total Sample (n=120)"

Discussion

The primary factor in both morbidity and mortality among hemodialysis patients with chronic kidney disease is CAD. Coronary artery disease has been related _ in cardiac and non-cardiac patients_ to the heart's epicardial fat thickness (EFT) and visceral fat (7).

EFT has been implicated as a cardiovascular risk in both the general population and those with chronic kidney disease. Furthermore, it has been proven that EFT acts more than other adipose tissues; EFT is a highly active organ that produces bioactive adipokines, pro-inflammatory, and proatherogenic cytokines (7).

The relationship between DN, visceral adipose tissue (VAT), and inflammation has been shown (5, 10). However, in the literature, a paucity of studies demonstrated the correlation between epicardial fat tissue (EFT) and albuminuria in patients with diabetes.

So, the current study aimed to estimate EFT's efficacy in predicting nephropathy, CAD, and DN by two dimensions of echocardiography. The study enrolled 120 patients, 101 diabetic patients, and 19 non-diabetic patients.

The main finding of our study was that EFT considered an independent risk factor for nephropathy (OR= 14.021, AUC= 0.494 with 67% accuracy at cut-off point> 0.65), CAD (OR= 10.081, AUC= 0.936 with 86.5% accuracy at cut-off point> 0.55) and affected vessels (OR= 14.021, AUC= 0.981 with 87.5% accuracy at cut-off point > 0.45 cm) in diabetic patients.

Also, we found that EFT was considered an independent risk factor for nephropathy (OR= 4.365, AUC= 0.601 with 72% accuracy at cut-off point> 0.45), CAD (OR= 18.635, AUC= 0.977 with 90.5% accuracy at cut-off point> 0.45) and affected vessels (OR= 8.826, AUC= 0.979 with 91.5% accuracy at cut-off point > 0.45 cm) in all studied patients.

The amount of EFT also rose with the stage of renal failure, according to earlier research. It is known that dialysis patients have more EFT than the average person. Furthermore, the authors found that eGFR was independently and negatively correlated with EFT volume, and based on this finding, they proposed that EFT could be a marker of the uremia-specific component of CV risk (11).

Additionally**, Akbas et al. (5)** showed that diabetic patients with EFT values more than 4.5 mm had albuminuria with a sensitivity of 70.6 percent and a specificity of 67.4 percent. Along with disease duration, HbA1c, and eGFR, EFT was discovered to predict albuminuria.

According to this study, advanced endothelial dysfunction brought on by proatherogenic, pro-inflammatory, and bioactive molecules secreted from epicardial fat tissue may cause increased albuminuria at higher EFT levels. Thus, there are connections between EFT, visceral adipose tissue, and inflammation. Furthermore, measuring EFT with echocardiography is more practical than CT and MRI and more accurate than VAT assessments using anthropometric measurements like waist circumference (5).

Additionally, a meta-analysis of nine studies involving more than 3500 patients found a relation between thickened EFT and CAD and a relation between high EFT and the progression of coronary plaque (12). The atherogenic effects of epicardial adipose tissue are due to its anatomic proximity to plaque and its vigorous pro-inflammatory activity. People with cardiovascular disease produce significantly higher pro-inflammatory adipokines from their

epicardial adipose tissue than their subcutaneous adipose tissue (7).

In a meta-analysis of more than 40,000 patients, EFT was an independent risk factor for CVD, and EFT was also related to calcification of coronaries and myocardial ischemia (11). According to certain recent studies, visceral adipose tissue accumulation is not the only risk factor for cardiovascular events. Still, EFT is an independent predictor of coronary events and left ventricular dysfunction (13-16).

It is shown that pathogenetic processes, inflammation, and insulin resistance are amenable to the mechanism by which EFT results in cardiovascular events. EFT simultaneously causes paracrine and autocrine effects with the inflammatory adipokines and cytokines it secretes. EFT is not always applied symmetrically around the heart. More people are developing atherosclerotic plaques, especially in regions with high EFT accumulation. This supports the hypothesis that EFT causes inflammation through paracrine effects (17-19).

Epicardial adipose tissue releases pro-inflammatory adipocytokines, including leptin, adipsin, TNF-, IL-1, IL-6, IL-18, and resistin, which cause a systemic inflammatory response. Epicardial adipose tissue builds up due to a positive feedback mechanism brought on by systemic inflammation. Our team's previous research found that concurrent inflammatory events brought on the correlation between EFT and CVD frequency (19-21).

Also, in accordance with the current study, **Jeong et al. (22)** found that epicardial fat thickness (OR 10.53, p = 0.004), diabetes mellitus (OR 8.06, p = 0.006), and smoking (OR 14.65, p = 0.015) were individual factors affecting coronary artery stenosis significantly. Also, **Kamal et al. (23)** declared that EFT was significantly correlated with the presence of CAD ($P < 0.001$) at a cut-off value of 5.5 mm. EFT was markedly correlated with the severity of CAD assessed by the Gensini score ($P < 0.001$).

According to Kamal et al. (23), the presence of CAD can be expected with high sensitivity and specificity at a cut-off value of 5.5 mm for EFT. **Faghihi et al. (24).,** found an EFT cut-off value of 2.95 mm in their study with a sensitivity of 83% and specificity of 75%. **Eroglu et al. (25)** had 85% sensitivity and 81% specificity at a cut-off point of 5.2 mm.

Recent research by **Majumder et al. (27)** revealed that smoking and EFT were independent risk factors for significant coronary artery stenosis (OR 2.66, p=0.03, and 6.07, p0.001, respectively). EFT > 4.65mm predicted the presence of significant coronary stenosis by ROC curve analysis with 76.1 percent sensitivity and 69.9 percent specificity. One thing to remember is that some researchers measured EFT at end-systole while others used end-diastolic frames, which may explain their differences.

The main limitations of the current study included a relatively small sample size and no long-term follow-up of those patients.

Conclusions*: The measurement of EFT using 2D echocardiography is a good prognostic tool for determining* the severity of CAD. Also, the number of affected coronary vessels was correlated with increased EFT. Epicardial fat is a good predictor of CAD, nephropathy, and the number of affected vessels.

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