Epicardial adipose tissue volume as a predictor of the severity of coronary artery disease by CCTA

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Abstract: Background: Epicardial adipose tissue has been proposed as a risk factor for coronary artery disease, as well as a predictor for the development of future cardiovascular events. Located between the myocardium and the visceral pericardium, EAT is visceral fat that directly surrounds the coronary arteries. **Aim of the Study:** The aim of the study is to evaluate the relationship between epicardial fat volume and the severity of coronary artery disease among patients presented by chest pain with low to intermediate pretest probability for CAD, using Multi-Slice CT coronary angiography. **Patients and Methods**: This study is the result of collaboration between National Heart Institute and el Hussein hospital which included 100 consecutive patients with suspected coronary artery disease referred for multi-slice CT angiography from May 2017 to May 2018. **Results**: there is positive correlation between epicardial adipose tissue scores that measure extent and severity of CAD plaque (Ca score, ABO score, SIS score, and SSS score) and atherosclerosis. **Conclusion**: there is a significant correlation between epicardial adipose tissue and coronary atherosclerosis and EFV increased steeply in patients with significant coronary artery stenosis as revealed by multi-detector computed tomography.

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1. Introduction

Obesity or excess amount of body fat is a well-established risk factor for coronary heart disease.

The distribution of body fat varies among individuals and may be as important as the amount of body fat in determining risk. In fact, excess accumulation of fat around the upper body is associated with a higher risk of coronary heart disease regardless of total body fat.

Waist circumference, reflecting abdominal obesity, is a risk factor of metabolic syndrome and coronary artery disease (CAD). Adipose tissue secretes many factors implicated in atherogenesis; however, the role of pericardial fat (ectopic visceral fat around coronary arteries) in the pathogenesis of CAD is not clear**.**

Fat depots in various parts of the body have different properties which may underlie the importance of fat distribution. For example, pericardial fat, the fat depot around the heart, releases more inflammatory cytokines than subcutaneous fat**.**

Inflammation has been linked to coronary heart disease. Furthermore, inflammation due to fat depots tends to be localized in their surrounding tissues and organs**.**

Epicardial adipose tissue (EAT) has been proposed as a risk factor for coronary artery disease (CAD), as well as a predictor for the development of future cardiovascular events. Located between the myocardium and the visceral pericardium, EAT is visceral fat that directly surrounds the coronary arteries. It may work as an endocrine organ secreting hormones, bioactive adipocytokines and chemokines, in this way potentially promoting CAD. Consequently, EAT may have a potential role as a parameter for risk stratification purposes in patients presenting with chest pain.

The development of atherosclerosis by lipoprotein storage, inflammation, muscle cell proliferation, necrosis, apoptosis, calcification, and fibrosis in the arterial wall triggers important changes in the coronary vessels, leading to coronary artery disease (CAD). In fact, atherosclerosis is the main etiology of CAD, and plaque rupture followed by intraluminal thrombosis is the most common cause of acute coronary events, including sudden coronary death. For that reason, the early and accurate characterization and quantification of atherosclerotic plaque is valuable for preventing and managing acute coronary syndrome.

Multi-slice CT is a noninvasive tool that allows to reliably assessing both obstructive and non-obstructive subclinical coronaryartery disease in an earlier stage than invasive angiography and providing data on calcium burden, the presence of coronary artery stenosis, but also, more recently, on coronary atherosclerotic plaque morphology and composition**.**

2. Patients and Methods

This study is the result of collaboration between National Heart Institute and el Hussein hospital which included 100 consecutive patients with suspected coronary artery disease referred for multi-slice CT angiography from May 2017 to May 2018.

All patients were subjected to:

A-Full history taking and thorough clinical examination.

B- Standard 12 lead resting ECG.

C- investigations: complete lipid profile, serum creatinine and random blood sugar.

D- Multi-slice CT angiography.

Statistical presentation and analysis of the present study was conducted using the mean, standard deviation, student *t*-test, Chi-square by SPSS V20 with $p<0.05$ means significance.

3. Results

This study is the result of collaboration between National Heart Institute and el Hussein hospital which included 100 consecutive patients 70 patients with plaque burden and 30 control normal patients who were referred to the MSCT coronary angiography unit.

Table (1) shows correlation between epicardial fat volume and risk factors for atherosclerosis.

Risk Factors (qualitative factors		EFV (cm3)					
		Mean	Standard Deviation	Median	Minimum	Maximum	*P* value
Sex	M	128.01	34.45	125.55	55.60	221.30	0.0021*
	F	83.55	21.73	88.55	47.40	103.60	
HTN	Y	140.29	34.19	138.55	82.50	221.30	< 0.001*
	N	111.54	30.78	111.60	47.40	182.60	
DM	Y	137.71	30.06	133.30	83.50	211.90	< 0.001*
	N	108.94	35.52	100.90	47.40	221.30	
Smoking	Y	124.25	30.11	124.30	55.60	221.30	0.754
	N	126.52	40.61	120.85	47.40	211.90	
Family history of CA	Y	139.44	30.07	129.80	104.00	204.50	0.082

Table (1) shows: Significant correlation between EFV and sex (P = 0.002) more in male than female (2) Highly significant correlation between EFV and hypertension (P <0.001) hypertensive patients have more EFV than non-hypertensive patients (3) Highly significant correlation between EFV and diabetes mellitus (p < 0.001) diabetic patients have more EFV than non-diabetic patients (4) Insignificant correlation between EFV and smoking (p = 0.754) (5) In significant correlation between EFV and family history of ischemic heart disease (p = 0.082).

***Table (2): Comparison between scores that measure extent and severity of CAD plaque and EFV of the two study groups.**

	group										
	group A					group B					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Ca score	11.65	29.87	.00	.00	103.60	215.87	404.83	90.00	.00	2212.00	< 0.001
ABO	.00	.00	.00	.00	.00	1.85	1.10	1.00	1.00	5.00	< 0.001
SIS score (16)	.37	.56	.00	.00	2.00	2.00	1.28	2.00	1.00	7.00	< 0.001
SSS score (48)	.80	1.21	.00	.00	4.00	5.49	3.57	5.00	2.00	20.00	< 0.001
EFV	93.17	24.48	88.95	47.40	149.60	136.96	30.72	133.60	86.80	221.30	< 0.001

The comparison showing significant correlation between EFV volume and scores that measure extent and severity of CAD plaque (Ca score, ABO score, SIS score, and SSS score) and atherosclerosis.

4. Discussion

Visceral adipose metabolism has proven to be important in the CVD development, indicating that each visceral body fat storage is anatomically and functionally different. Moreover, according to the

closeness of the fat tissue to an organ, it exerts a specific local function for each one.

This study aimed to investigate the relationship between epicardial fat volume and atherosclerosis as well as other risk factors of atherosclerosis.

Contrast-enhanced high-resolution computed tomography (CT) scans of the coronary arteries allow the evaluation not only of the degree of coronary stenosis, but also coronary plaque classification, coronary calcium scoring and epicardial fat volume evaluation.

Our study was conducted in national heart institute. It included 100 consecutive patients referred for MDCT along with full labs including renal function tests and lipid profile. The mean age of the studied population is 56.03 ± 10.24 years.

While analyzing the data obtained from the current study it is important to keep in mind the study population characteristics. All study group was presented by chest pain with low to intermediate pretest probability.

In our study, we used scores to measure extent and severity of atherosclerosis in coronaries (SIS, SSS, ABO and Ca score).

The study showed that EFV was significantly associated with both coronary atherosclerosis and coronary artery stenosis.

EFV increased step-wise with increased coronary plaque burden (increased coronary segments containing plaques) and increased steeply with the presence of significant coronary artery stenosis, defined as percent diameter stenosis >50%. Also in this study dyslipidemia was significantly associated with increased epicardial fat volume, especially LDL.C, HDL.C and total cholesterol.

Okada et al. (2014) analyzed the relationship between the volume of EAT and the severity of coronary artery disease in non-obese patients as well as the potential effect that the epicardial fat volume has on coronary plaque morphology or the extension. Individuals with increased volume of EAT had a higher severity in coronary level plaques, which were not necessarily calcified, indicating that the thickness storage of epicardial fat has a key role in the progression of coronary atherosclerotic disease, even in those individuals with no accumulation of visceral fat. In addition, correlations between increased EAT and reduced HDL-C and increased IL-6 and high sensitivity C-reactive protein (hs-CRP) were observed. our study showed that EFV was significantly associated with both coronary atherosclerosis and coronary artery stenosis the HDL.C was significant risk factor and epicardial fat volume is inversely proportional to its increase.

Mahabadi et al. (2013) sought to determine whether epicardial fat volume predicts coronary events in the general population. Incident coronary events were assessed during a follow-up period of 8.0 ± 1.5 years. Multivariable association of EAT with cardiovascular risk factors, coronary artery calcification (CAC), and coronary events was assessed using regression analysis. From the overall 4,093 participants (age 59.4 years, 47% male), 130 subjects developed a fatal or nonfatal coronary event. Incidence of coronary events increased by quartile of EAT (0.9% vs. 4.7% for 1st and 4th quartile, respectively, $p < 0.001$). Doubling of EAT was associated with a 1.5-fold risk of coronary events when adjusting for cardiovascular risk factors (hazard ratio [HR] [95% confidence interval (CI)]: 1.54 [1.09 to 2.19]), which remained unaltered after further adjustment for CAC score (HR [95% CI]: 1.50 [1.07 to 2.11]). Epicardial fat is associated with fatal and nonfatal coronary events in the general population independent of traditional cardiovascular risk factors and complements information from cardiac computed tomography above the CAC score. This came in agreement with our study which showed that EFV is significantly associated with both coronary atherosclerosis and coronary artery stenosis leading to hazardous cardiovascular events, but we were different in MSCT was conducted on patients with suspected CAD not on general population.

Akyol et al. (2013) observed in teenagers with obesity and metabolic syndrome a close relationship between EAT, the thickness of the carotid intima, and early cardiac dysfunction parameters showing the predictive role of lipid accumulation for the adult and elderly population. Our study showed that increased BMI, serum cholesterol, LDL, LDL/HDL ratio and serum triglycerides were significantly associated with increased epicardial fat volume.

Bastarrika et al. (2010) included Forty-five individuals underwent cardiac dual-source CT and conventional coronary angiography for suspicion of CAD. Nonenhanced images acquired to assess calcium score were used to quantify EAT. Coronary stenosis grading was performed on conventional coronary angiograms using Gensini scores. Two independent observers manually measured right ventricular EAT thickness at three different levels and in two different planes (four chamber and short axis) to obtain mean values. Additionally, EAT volume was automatically determined using a commercially available software tool. Conventional coronary angiography demonstrated nonstenotic coronary arteries in 22 subjects and significant coronary artery stenosis in 23. Significant correlations were observed between volumetric estimation of EAT and body mass index, coronary artery calcification, and Gensini score. On automatic volumetry, patients with significant coronary artery stenosis had significantly greater EAT

volumes (154.58 ± 58.91 mL) than those without significant CAD (120.94 ± 81.85 mL). The patients with significant coronary artery stenosis had significantly greater EFV assessed by MSCT than those without significant CAD and this was found in our study.

Park et al. (2010) analyzed Effects of Statins on the epicardial fat thickness in patients with coronary artery stenosis. The use of statins, particularly atorvastatin, is associated with a reduction in the volume of EAT in patients with CAD; EAT change was 0.47 ± 0.65mm in the atorvastatin group versus 0.12 ± 0.52mm in the simvastatin/ezetimibe group. Our study showed that increase serum cholesterol and LDL (which are controlled by statins) were directly proportional to EFV.

Previous studies using echocardiography showed contradictory results between epicardial fat and CAD ***(Chaowalit et al., 2006) (Jeong et al., 2007) (Hirata et al., 2015)***.

Chaowalit et al. (2006) performed clinical study to confirm the association between EAT and the presence and severity of CAD in 139 patients; however, they failed to demonstrate the association with the severity of CAD.

Jeong et al. (2007) showed the relationship between echocardiographic EAT and CAD in 203 patients who underwent echocardiography and coronary angiography. Coronary angiograms were analyzed for the extent and severity of CAD using Gensini score. The patients with a higher epicardial fat thickness were associated with a high Gensini score (P = 0.014). Multivariate analysis showed that age (odds ratio (OR): 5.29, P = 0.003), epicardial fat thickness (OR: 10.53, P = 0.004), diabetes (OR: 8.06, P = 0.006), and smoking (OR: 14.65, P = 0.015) were independent factors affecting significant coronary artery stenosis. Interestingly, EAT was significantly correlated with the extent and severity of CAD, as assessed by the Gensini score.

Gorter et al. (2008) demonstrated that volumetric quantification of epicardial fat using cardiac CT is highly reproducible compared with more simple measurements such as epicardial fat thickness and area. In this study we used the volumetric quantification to measure the epicardial fat volume by MSCT.

Rosito et al. (2008) in a sub study of the Framingham Heart Study, found that epicardial fat was correlated with multiple measures of adiposity and cardiovascular disease risk factors. They also found that epicardial fat was associated with coronary artery calcification, whereas intrathoracic fat was associated with abdominal aortic calcification.

De Vos et al. (2008) showed that pericoronary epicardial fat thickness using cardiac CT was strongly related to vascular risk factors and coronary calcification in postmenopausal women. The positive correlation between epicardial fat and the number of metabolic alterations suggests that epicardial fat might be a valuable quantitative marker of metabolic impairments and systemic atherosclerosis, and provides us with a clue to risk stratification for CAD.

Recent studies investigated the relationship between epicardial fat volume using cardiac CT and severity of CAD**.** Although they found a modest relationship between epicardial fat volume and CAD severity, most studies did not find stepwise increase of epicardial fat volume with increasing severity of coronary atherosclerosis***).***

Gorter et al. (2008) measured epicardial adipose tissue volume using cardiac CT in 128 patients and found that it was not correlated with the severity of coronary atherosclerosis and the extent of coronary artery calcification, although they found the relationship in patients with body mass index <27. In our study the BMI was significant risk factor and epicardial fat volume is directly proportional to it and not limited to the results <27 and this may be due to characteristics of the patients of the study group and other risk factors association.

Djaberi et al. (2008) found that epicardial adipose tissue volume using cardiac CT did not increase with increasing severity of atherosclerosis despite significant relation between epicardial adipose tissue volume and presence of coronary atherosclerosis**.** In contrast, our results showed that epicardial fat volume was significantly higher in patients with severe coronary artery stenosis compared with those without coronary artery stenosis.

Ueno et al. (2009) found that increased epicardial fat volume was the strongest independent determinant of the presence of totally occluded lesions. In our results found that epicardial fat accumulation is correlated to increasing severity of coronary atherosclerosis and the development of severe coronary artery stenosis.

Lisa et al. (2011) measured the epicardial fat volume using cardiac MRI in asymptomatic persons and it was correlated more strongly with plaque burden than body mass index (BMI). However, data about epicardial fat in asymptomatic individuals was limited, partially because the primary assessment method, intravascular ultrasound, was invasive. In contrast our study using cardiac CT was conducted on patients with suspected CAD.

Conclusion:

Our results showed that EFV was associated with coronary atherosclerosis and EFV increased steeply in patients with significant coronary artery stenosis and

in those with severe coronary artery calcification as revealed by multi-detector computed tomography.

Quantitation of EFV may be useful, in addition to coronary artery calcium score and can be used as a predictor to identify patients at risk for CAD.

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No conflicts of interest declared.

Authors' Contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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