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ORIGINAL RESEARCH

The Assessment of Epicardial Adipose Tissue in Acute Coronary Syndrome Patients. A Systematic Review

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ABSTRACT

Background: This systematic review seeks to evaluate the role of epicardial adipose tissue (EAT), quantified either by thickness, assessed by transthoracic echocardiography, or by volume, assessed by cardiac computed tomography (CT), in the follow-up of patients with acute coronary syndromes (ACS). **Method:** One-hundred forty-four articles were screened, from which 56 were reviewed in full-text. From those, 47 studies were excluded for the following reasons: they did not meet the inclusion criteria; they were either reviews or meta-analyses; the study cohorts included only stable coronary artery disease patients; they did not state a clear and concise study design, endpoints, or follow-up. The final draft included nine studies for systematic evaluation. **Results:** Of the 2,306 patients included in the review, 170 underwent cardiac CT while the remaining 2,136 underwent transthoracic echocardiography for the measurement of EAT. The analysis found that the EAT thickness was significantly associated with major adverse cardiovascular events (MACE) rates during hospitalization (OR: –1.3, 95% CI: 1.05–1.62, p = 0.020) and at three years (HR: 1.524, 95% CI: 1.0–2.2, p = 0.038). The included studies found that EAT was correlated with the following clinical and angiographic risk scores for ACS: GRACE (r = 0.438, p <0.001), TIMI risk score (r = 0.363, p = 0.001), SYNTAX score (r = 0.690, p <0.0001; r = 0.610, p <0.01), and Gensini score (r = 0.438, p = 0.001). There was an inverse correlation between ST-segment resolution of <70% after revascularization and EAT (r = -0.414, p = 0.01), and the myocardial blush grade (r = -0.549, p <0.001). The EF aggregation ranged between 2.65 mm and 4.7 mm within the included studies. **Conclusions:** EAT, evaluated either by echocardiography or cardiac CT, correlates with the severity of coronary lesions, with the clinical and angiographic risk scores for acute coronary syndromes, with indicators for coronary reperfusion, and with short- and long-term MACE rates. Further studies are required to fully elucidate the role of this extensively studied but still novel cardiovascular biomarker as part of a risk prediction tool.

Keywords: epicardial adipose tissue, acute coronary syndromes, echocardiography, cardiac CT

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INTRODUCTION

Acute coronary syndromes remain a leading cause of death worldwide despite the many advances in both preventive strategies and emergency treatment options, including percutaneous coronary interventions.[1]

Several predictors of the severity of coronary artery disease have been established, and, in recent years, attention has been directed towards the role of epicardial adipose tissue (EAT) as a cardiovascular risk factor, as well as the assessment of instability of atherosclerotic coronary plaques.[2]

EAT – ROLE AND PATHOPHYSIOLOGY

Adipose tissue surrounding the heart has several roles, including being an energy provider for myocardial metabolism, thermoregulation, and mechanical protection for both the epicardial coronary vessels and the autonomic innervation of the heart.[3] The metabolic and immunologic effects of EAT remain unclear, although several hypotheses have been suggested, including that of secreting increased quantities of anti- and pro-inflammatory cytokines, regulating the oxidative reactions within the myocardial fibers, as well as influencing the contractility, conductibility, and excitability of the heart.[4]

Furthermore, being a visceral fat and having the same characteristics and behavior as intra-abdominal fat, EAT appears to be one of the extra-vascular culprits associated with the progression and aggravation of atherosclerotic lesions.[5]

The genesis of a coronary atheroma is influenced, in various stages, by the adipose tissue surrounding the heart, from intimal malfunction at an early stage, to plaque erosion and rupture, with subsequent thrombosis and the occurrence of an acute coronary syndrome.[6,7]

Histopathological studies of epicardial fat samples acquired during cardiac surgery have shown that EAT contains several inflammation biomarkers, including tumor necrosis factor-α, interleukins, and chemokines, which might contribute to the development and progression of insulin resistance, and also enhance apoptosis within the coronary plaque and vessel inflammation.[8]

On the other hand, epicardial adipose tissue has beneficial effects by secreting adiponectin — with anti-inflammatory and anti-atherogenic properties and also by stimulating neo-angiogenesis in subjects with chronic coronary occlusions.[8,9]

EAT IN CORONARY ATHEROSCLEROSIS AND ACUTE CORONARY SYNDROMES

EAT has been shown to be linked with the presence and severity of coronary atherosclerotic lesions.[10,11] Subjects with an increased EAT, assessed either by echocardiography or cardiac CT, have a more severe extension of coronary atherosclerosis, and EAT is also linked to the overall plaque burden and cardiovascular risk factors.[12–14] Furthermore, the incidence of myocardial infarction seems to be directly proportional to the increase in epicardial fat, which is also related to a higher rate of major adverse cardiovascular events in subjects with known coronary artery disease (CAD).[15,16] Due to its paracrine properties, by secreting serum inflammatory biomarkers EAT brings a significant contribution to the vulnerability of the coronary atheromatous plaque, either by local inflammation or by stimulating neo-angiogenesis and the development of vasa-vasorum and subsequent intra-plaque hemorrhage, plaque rupture and thrombosis.[15,17,18] Patients without chest pain who present with major adverse cardiovascular events have a bigger epicardial fat volume compared to event-free patients.[19] The coronary artery calcium score, a marker of CAD severity, has a positive correlation with EAT in patients with both obstructive and non-obstructive CAD. An increased EAT volume, together with low attenuation plaques with the presence of a napkin-ring sign, are correlated with a higher risk of future acute coronary events in non-obese subjects.[20,21] Moreover, the thickness of the epicardial fat has been shown to be closely linked to the presence of multi-vessel CAD in patients with acute myocardial infarction.[22]

EAT – METHODS OF ASSESSMENT AND IMAGING TECHNIQUES

The imaging methods for assessing epicardial fat include 2D transthoracic echocardiography (TTE), native cardiac computed tomography and magnetic resonance imaging (MRI).[23] MRI remains the gold-standard technique for measuring not only the adipose tissue surrounding the heart but also the total visceral fat. Despite the fact that MRI allows the acquisition of high-resolution images and the possibility of quantifying EAT volume, it is not feasible in an emergency clinical setting, as it is more costly and less available than other methods.[24]

Transthoracic 2-dimensional echocardiography is a low-cost and easily available, non-invasive method that allows the quantification of epicardial fat. It has been proven to be as useful as more advanced imaging meth-

ods such as CT or MRI.[25] The 2-D TTE measurement of epicardial fat thickness is expressed in millimeters and is performed with the patient in a lateral decubitus position, at the level of the free wall of the right ventricle, from a parasternal long axis view, in three consecutive cardiac cycles, at the end-diastolic period.[26] EAT is illustrated on TTE as a hypoechoic space between the epicardium and pericardium. The consensus of opinion is that a value of >5 mm should be considered suggestive of an increased EAT.[23,26–29] TTE assessment of EAT has several limitations, including inter- and intra-observer variability, as well as the location of epicardial fat on the surface of the heart and the phases of the cardiac cycle in which the measurements are done.[30] Further drawbacks include problems in discriminating between epicardial and pericardial material or fluid in the pericardial sack.[26]

Cardiac computed tomography (CT) examination can accurately assess the volume, total area, and thickness of epicardial adipose tissue, and concomitantly it can evaluate coronary atheromas and their degree of calcification.[23,31] EAT can be measured by CT at the level of the free wall of the right ventricle, in the atrioventricular and interventricular spaces, and also in the proximity of the main coronary vessels, when it is regularly associated with coronary calcium score evaluation.[23] Similarly to TTE assessment, EAT volume measured by CT does not have a precise range considered as normal. A study (2008) stated the average EAT volume was 110 ± 41 ml in females and 137 ± 53 ml in males,[32] and Shmilovich *et al.* (2011) reported that epicardial fat volume indexed to the whole body surface area, at the 95th percentile, was 68.1 ml/m2.[33] The limitations of this technique are represented by the difficulty of achieving standard location limits for the measurements and by the inter-observational variability.[34,35]

MATERIALS AND METHOD

SEARCH STRATEGY

The study was conducted in agreement with the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[36]

The literature search was centered on accessing all published articles related to epicardial adipose tissue evaluation in acute coronary syndrome patients, either by TTE or cardiac CT.

Two investigators searched the PubMed/Medline and Thomson Reuters scientific databases. The comprehensive search strategy comprised the following medical subject headings (MeSH) terms: "epicardial fat AND acute coronary syndromes", "epicardial adipose tissue AND acute coronary syndromes", "epicardial fat thickness", "epicardial fat volume".

DATA EXTRACTION AND ANALYSIS

The two investigators extracted the following data from the selected manuscripts: the number of subjects included in the study, age, gender, type of acute coronary syndrome for which they had been admitted, the follow-up period, the primary and secondary endpoints, the method of assessment of EAT, the mean values (TTE) and volume (cardiac CT) of EAT respectively, as well as the presence of diabetes, smoking, hypertension history, obesity. Furthermore, whenever available, data extraction included the odds ratios (OR) and hazard ratios (HR) when appropriate for the endpoints of each study.

STUDY QUALITY ASSESSMENT AND ELIGIBILITY CONDITIONS

No study was excluded for motives of decreased study quality, but the selected studies presented a concise portrayal of the inclusion and exclusion criteria, the endpoints and the follow-up periods, as well as a precise method for assessing the EAT, irrespective of the non-invasive method that had been used (TTE or cardiac CT). Articles that enrolled only subjects with stable CAD were excluded from the search. Also, we excluded various articles such as case reports, case series, reviews, editorials, letters, as well as manuscripts that were not available in full-text form. The search filter also excluded species other than humans.

RESULTS

One-hundred forty-four manuscripts were screened in total, out of which 56 were identified using the described search strategy and were reviewed in a full-text form. From those, 47 studies were excluded for not meeting the inclusion criteria. These were either reviews or meta-analyses, the study cohorts included only stable coronary artery disease patients, or they did not state a clear and concise study design, endpoints or follow-up (Figure 1). The final draft included nine studies for systematic evaluation: one study that used CT for EAT assessment, and eight manuscripts that assessed EAT with TTE.

In all, 2,306 patients were included, of which 170 subjects underwent cardiac CT for EAT evaluation,[37] while the remaining 2,136 patients underwent TTE measure-

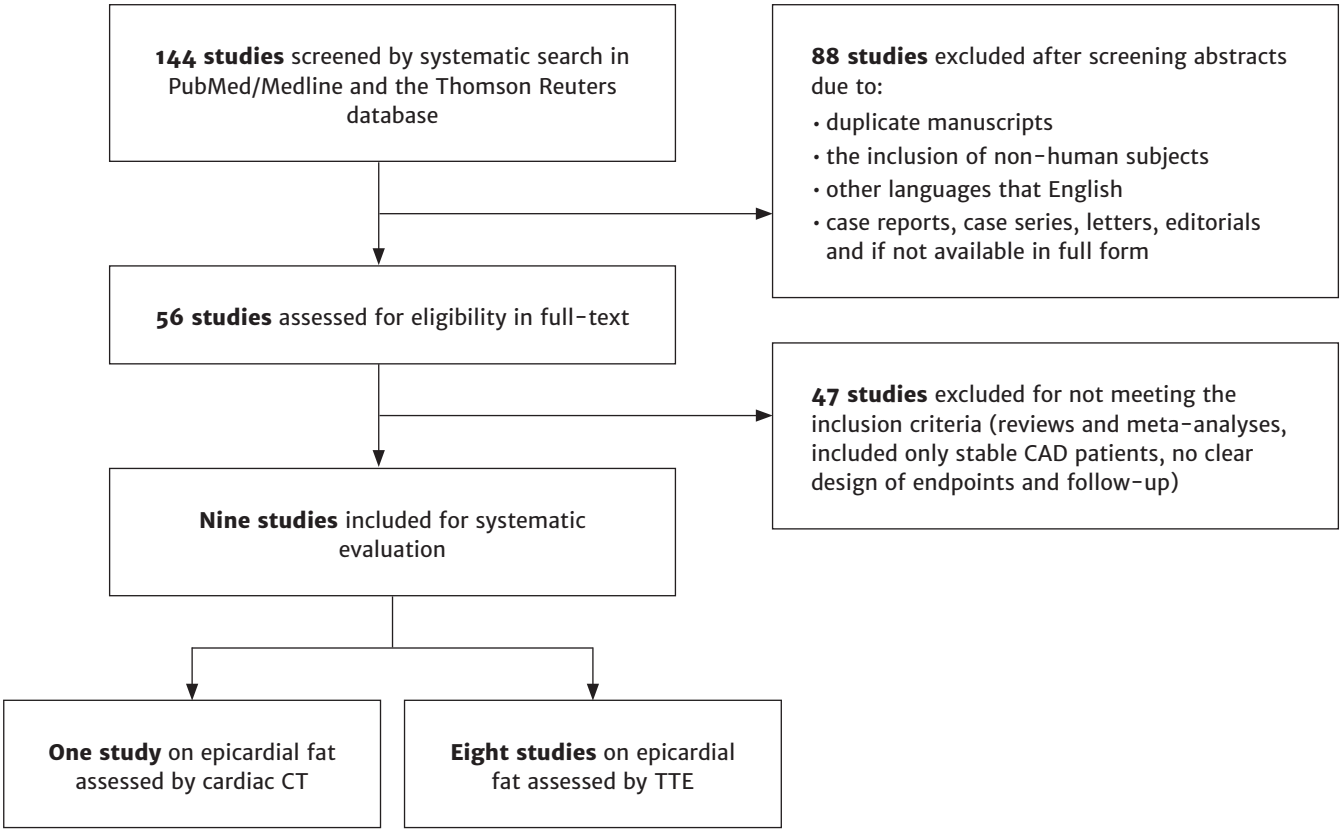

FIGURE 1. Diagram of the search protocol and results of manuscript selection

ment of EAT.[38–45] Table 1 presents a summary of the included manuscripts. All systematized manuscripts contain a concise and clear portrayal of the inclusion and exclusion criteria and the method for assessing EAT, either through cardiac CT or TTE (Table 1). All studies enrolled patients with acute coronary syndromes. Six of the nine studies used, as one of the main exclusion criteria, previous revascularization therapies, either by coronary artery bypass grafting or percutaneous coronary intervention.

CHARACTERISTICS OF THE STUDY POPULATIONS

The overall characteristics of the patients included in the nine study cohorts, including cardiovascular risk factors and gender distribution, are listed in Table 2.

STATISTICAL ANALYSIS AND STUDY DESIGN OF THE SELECTED MANUSCRIPTS

There was a diversity of study methodology and statistical approaches used in the selected manuscripts. Four studies were retrospective and calculated odds ratios based on multivariate logistic regression. From the five prospective observational studies, only one used Cox proportional hazards models for the prediction of major adverse cardiovascular events (MACE) rates during the three-year follow-up.[42] Most researchers (n = 6) used the Receiver Operator Characteristics (ROC) curve and the area under the curve for the determination of the cut-off value for EAT values that predicted the study outcome.[37–41,45] All selected articles used Spearman or Pearson correlation coefficient statistics for evaluating the link between epicardial fat and other clinical and laboratory variables.

STUDY ENDPOINTS AND RESEARCH HYPOTHESES

EAT and MACE

Two manuscripts examined the prognostic value of EAT, and the endpoints included the in-hospital MACE rates.[40] One study42 had a three-year follow-up period, with major adverse cardiovascular events as a primary endpoint. Both survival studies included multivariate adjustments for cardiovascular risk factors (smoking, diabetes, age) as well as medical history (previous cardiovascular and

TABLE 1. Summary of the included studies

Authors (*ref)	Year	Inclusion criteria	Exclusion criteria	Follow-up	Research hypothesis
Studies that assess the EFV (ml) by using cardiac CT					
Harada *et al.*[37]	2011	ACS patients (STEMI and NSTEMI)	• previous revascularization (CABG or PCI)	None	Higher EFV in patients with ACS
Studies that assess EFT (mm) by using transthoracic echocardiography					
Altun *et al.*[38]	2013	ACS patients (STEMI and NSTEMI)	• poor quality images on TTE • history of CABG • CKD • severe valvular disease	None	Correlation of EFT with GRACE and SYNTAX scores
Tanindi *et al.*[39]	2015	• stable angina patients • ACS patients	• previous revascularization (CABG or PCI) • pericardial effusion • more than moderate valvular disease • poor quality images on TTE	None	EFT with impaired coronary perfusion evaluated with MBG and TCF
Wang *et al.*[40]	2014	AMI patients with: • normal thoracic shape • sinus rhythm • no severe respiratory diseases	• previous revascularization (CABG or PCI) • CKD with GFR <30 ml/min • severe hydro-pericardium • poor quality images on TTE	None	Composite of major in-hospital events – cardiac death, acute heart failure, repeated revascularization, recurrent MI or ischemia
Sen *et al.*[41]	2015	STEMI patients undergoing PCI	• recent MI • previous revascularization (CABG or PCI) • presentation after >12h from symptom onset • severe hepatic and kidney disorders • neoplastic diseases	None	Correlation between EFT and IRA patency at presentation evaluated with the TIMI flow grading system
Tscharre *et al.*[42]	2016	ACS patients (STEMI and NSTEMI)	• poor quality images on TTE • the impossibility of obtaining the long parasternal axis view on TTE	3 years	MACE rates (cardiovascular death, non-fatal MI, non-fatal stroke)
Gul *et al.*[43]	2015	Patients with first occurrence of NSTEMI	• chronic pulmonary and hepatic disorders • systemic inflammatory diseases • chronic myopathies • CKD (creatinine >2.5 mg/dl) • myocarditis and cardiomyopathies • congestive heart failure	None	Correlation between EFT and GRACE score
Özcan *et al.*[44]	2013	NSTEMI and USAP patients	• rheumatic diseases • neoplastic disorders • active infections • persistent ST elevation MI • history of HF with low EF <40% • poor quality images on TTE	None	Association between EFT and TMI risk score
Zencirci *et al.*[45]	2014	First acute STEMI patients who underwent primary PCI	• left ventricular hypertrophy (ECG Sokolow-Lyon index of >35 mV) • left bundle branch block • temporary or permanent pacing	None	Relationship between ST-segment resolution after pPCI and EFT

EFV – epicardial fat volume (ml); EFT – epicardial fat thickness; CABG – coronary by-pass grafting; PCI – percutaneous coronary intervention; CAD – coronary artery disease; ACS – acute coronary syndromes; CKD – chronic kidney disease; BMI- body mass index; TTE – transthoracic echocardiography; MBG – myocardial blush grade; TCF – thrombolysis in myocardial infarction frame count; IRA – infarct-related artery; USAP –unstable angina pectoris.

TABLE 2. Patient characteristics of the study population in the included manuscripts

Authors (*ref)	Total number of subjects enrolled	Gender (male) n (%)	Age (years)	BMI (kg/m²)	Diabetes n (%)	Smoking n (%)	Hypertension n (%)	Dyslipidemia n (%)
Studies that assess the EFV (ml) by using cardiac CT								
Harada *et al.*[37]	170	120 (70.5%)	63.5 ± 11.5	24.25 ± 3.25	nr	60 (35.2%)	nr	nr
Studies that assess EFT (mm) by using transthoracic echocardiography								
Altun *et al.*[38]	65	60 (92.3%)	57.4 ± 12.2	26.0 ± 2.07	22 (33.8%)	nr	27 (41.5%)	nr
Tanindi *et al.*[39]	200	160 (72.3%)	60.66 ± 13.33	27.7 ± 3.2	64 (28.9%)	99 (44.7%)	119 (53.8%)	107 (48.4%)
Wang *et al.*[40]	373	310 (83.1%)	66 ± 12	nr	99 (26.5%)	194 (52.0%)	209 (56%)	nr
Sen *et al.*[41]	640	523 (81.7%)	53.9 ± 9.7	26.0 ± 4.5	336 (52.5%)	354 (55.3%)	286 (44.6%)	305 (47.6%)
Tscharre *et al.*[42]	438	293 (66.9%)	nr	nr	nr	nr	nr	nr
Gul *et al.*[43]	162	115 (70.9%)	63.9 ± 12.8	27.6 ± 4.05	54 (33.3%)	85 (52.4%)	84 (51.8%)	nr
Özcan *et al.*[44]	144	101 (70.1%)	62.55 ± 11.4	28.1 ± 4.1	49 (34.0%)	71 (49.3%)	76 (52.7%)	nr
Zencirci *et al.*[45]	114	99 (86.8%)	54 ± 10	27.65 ± 3.55	23 (20.1%)	63 (55.2%)	40 (35.0%)	nr

Values are listed as mean ± standard deviation, or as a median
nr – not reported

TABLE 3. Prognostic value of epicardial fat thickness assessed by transthoracic echocardiography

Authors (*ref)	Time of Endpoint evaluation	Outcome	Events n (%)	EFT aggregation	OR (95% CI)	HR (95% CI)	P value	Multivariate Adjustments
Wang *et al.*[40]	Hospitalization index	In-hospital MACE	55 (14.7%)	4.7 mm	1.3 (1.05–1.62)	–	0.020	Diabetes, smoking, previous myocardial infarction, age
Tscharre *et al.*[42]	3 years	MACE	64 (14.6%)	2.65 mm	–	1.524 (1.0–2.2)	0.038	Statin therapy, age, AF, Previous MI, previous stroke, HF, diabetes

MACE – major adverse cardiovascular events; MI – myocardial infarction; HF – heart failure

TABLE 4. EFT and risk scores for acute coronary syndrome

Study	Risk score	Risk score value	EFT aggregation	Correlation coefficient r/β	P value
Altun *et al.*[38]	GRACE	101.8 ± 33.1	5.5 mm	0.224	0.072
	SYNTAX	11.5 ± 5.6	5.5 mm	0.690	<0.0001
Tanindi *et al.*[39]	MBG	1.7 ± 1.16	>7 mm	-0.549	<0.001
	TFC	35.02 ± 7.7	>7 mm	0.757	<0.001
Sen *et al.*[41]	TIMI flow	0, 1, 2 – impaired coronary flow	5.6 ± 1.84 mm	nr	0.001
Gul *et al.*[43]	GRACE	nr	4.68 mm	0.438	<0.001
Özcan *et al.*[44]	TIMI RS	5.2	8.2 ± 2.1 mm	0.363	0.001
	Gensini	54.3 ± 17.5	8.2 ± 2.1 mm	0.442	0.001
Zencirci *et al.*[45]	ST segment resolution after PCI (ΔSTR)	<70%	5.5 ± 2 mm	-0.414	0.01
Wang *et al.*[40]	SYNTAX	≥33	4.7 mm	0.610	<0.01

GRACE – global registry of acute coronary events risk score; SYNTAX -; MGB – myocardial blush grade; TFC – TIMI frame count; nr – not reported; TIMI RS – thrombolysis in myocardial infarction risk score; PCI – percutaneous coronary intervention; ΔSTR – difference between the sum of ST segment elevations before and after revascularization

cerebrovascular events, heart failure) (Table 3). Wang *et al.* (2014) showed that there is a significantly higher rate of MACE during hospitalization for acute myocardial infarction in patients with an EAT thickness of >4.7 mm (p = 0.02) after multivariate adjustments.[40] The other study on the prognostic value of EAT, on ST-elevation myocardial infarction (STEMI) versus non-ST-elevation myocardial infarction (NSTEMI) patients, revealed that a median EAT thickness of 2.6 mm (interquartile range 2.00–3.00) had a significant predictive capacity for the primary endpoint on both univariate (HR: 1.479, 95% CI: 1.192–1.953, p = 0.006) and multivariate (HR: 1.524, 95% CI: 1.011–2.267, p = 0.038) Cox regression analysis.[42]

EAT and ACS risk scores

Seven manuscripts evaluated the correlation between EAT (measured with TTE) and various ACS risk scores (Table 4).[38–41,43–45] Zencirci *et al.* (2014) hypothesized that there is an inverse association between the EAT and the ST-segment resolution following primary PCI for acute STEMI.[45] Other studied risk scores are the SYNTAX score for coronary atherosclerosis severity, the GRACE and TIMI risk scores for survival following an acute cardiac event, and also indicators for coronary perfusion after PCI (TIMI flow, myocardial blush grade – MBG, and TIMI frame count – TFC) (Table 4).

The overall results of the manuscripts that evaluated risk scores state that there are statistically significant correlations between an increased EAT thickness and enhanced integer values of the calculated risk scores and low perfusion indicators.

EAT and acute coronary syndromes

Of the 2,306 patients, 1,527 presented with STEMI, 378 with NSTEMI, and thirty-four with unstable angina pectoris. Furthermore, two of the manuscripts included, in addition to patients with ACS, stable angina pectoris patients or subjects with suspected CAD, which acted as a control group.[37,39] Harada *et al.* (2011) evaluated EAT using cardiac CT and compared epicardial fat volume (EFV, ml) in subjects with ACS (n = 80) and controls (n = 90). There was no significant coronary artery stenosis, and healthy individuals had a significantly lower EFV compared to the case lot (p <0.001). Tanindi *et al.* (2015) showed that patients with AMI have a significantly higher EAT thickness compared to unstable angina or stable CAD patients (p <0.001)[39] (Table 5).

EAT assessed by TTE was variable among study measurements, the mean ranging from a minimum of 2.65 mm, to a maximum of 8.5 ± 1.4 mm (Table 5).

DISCUSSIONS

Although study design in the available research articles was not constant, the prognostic value of EAT in ACS and the possible correlations between EAT and ACS risk scores and coronary perfusion indicators were appraised. Despite not being consistent, the results indicated that EAT tends to negatively impact the outcome, the risk of further adverse events, and the success of coronary revascularization procedures.

The role of epicardial fatty tissue has been extensively studied, and its pathophysiology is now better known, showing both positive and negative bearings on the development and progression of CAD.[3–9]

TABLE 5. Epicardial fat thickness or volume in acute coronary syndromes

Authors	STEMI		NSTEMI		USAP		Total ACS		Stable SAP/controls*		P value
	n	EF	n	EF	n	EF	n	EF	n	EF	
Harada *et al.*[37]	51	na	29	na	na	-	80	117 ± 47 ml	90	95 ± 33 ml	<0.001 (ACS vs. Controls)
Altun *et al.*[38]	40	na	25	na	na	-	65	5.5 ± 0.5 mm	na	-	na
Tanindi *et al.*[39]	16	8.5 ± 1.4 mm**	17	8.5 ± 1.4 mm**	34	6.3 ± 1.8 mm	67	7.4 ± 1.6 mm	133	5.4 ± 1.9 mm	<0.001 (SAP-USAP vs. SAP-AMI vs. USAP-AMI)***
Wang *et al.*[40]	373	4.5 ± 1.05 mm	na	-	na	-	na	-	na	-	na
Sen *et al.*[41]	640	5.26 ± 1.96 mm	na	-	na	-	na	-	na	-	na
Tscharre *et al.*[42]	293	nr	145	-	na	-	528	2.65 mm	na	-	na
Gul *et al.*[43]	nr	-	162	5.0 ± 1.15 mm	na	-	na	-	na	-	na
Özcan *et al.*[44]	nr	-	na	-	na	-	144	7.2 ± 2.15 mm	na	-	na
Zencirci *et al.*[45]	114	4.65 ± 1.85 mm	na	-	na	-	na	-	na	-	na

na – not available; STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST elevation myocardial infarction; USAP – unstable angina pectoris; ACS – Acute coronary syndrome; SAP – stable angina pectoris; EF – epicardial fat assessed either as volume (ml) or as thickness (mm);
* Controls – patients with no significant coronary artery stenosis, with or without chest pain.
** The study analysed patients with acute myocardial infarction without differentiating between STEMI and NSTEMI patients, the mean EF is expressed for the total AMI patients (STEMI+NSTEM)
*** AMI includes both STEMI and NSTEMI.

There is evidence that EAT is in direct relation with the body mass index and the presence of obesity, and it is also increased in patients with metabolic syndromes.[32,46–48]

Epicardial fat has also been linked to an increased systemic inflammatory status in type 2 diabetes patients with acute myocardial infarction, and in patients with a higher EAT thickness it was associated with an enhanced left ventricular remodeling process and lower ejection fraction at six months.[49]

Further studies are needed to elucidate the effect of a reduction of EAT on risk diminution, although some researchers have proved that the regression of EF can be achieved with weight loss measures, dietary modifications, regular physical exercise, and lipid-lowering therapies with statins and ezetimibe.[28,50–52]

Coronary artery plaque burden was shown to be associated with a higher quantity of epicardial fat.[53] Several studies have stated that there is a relationship between an increased EAT and plaque vulnerability.[54–56] Noninvasive imaging biomarkers, identified by computed tomography coronary angiography, include the coronary artery calcium score, low-density plaques with an increased necrotic core, the presence of spotty calcifications and the napkin-ring sign.[57,58] Biomarkers for plaque instability, detected by advanced imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) include the thick fibrous cap atheroma, fibrous cap thickness, the extent of intra-plaque macrophage deposition, vessel extension and rupture.[59–61]

Two of the largest EAT studies included cohorts of patients with no cardiovascular disease. The MESA trial/study showed a positive association between the coronary artery calcium score and the EFV assessed by CT, but the Heinz-Nixdorf Recall study found that EAT predicted an excessive risk for coronary events, independently of the calcium score and classic cardiovascular risk factors.[15,62] The studies analyzed in our systematic review did not include manuscripts that had evaluated coronary calcium or vulnerable plaque biomarkers, as these did not meet the inclusion criteria.

EAT AND ACS RISK SCORES

Ongoing research is being undertaken to identify additional risk markers which could predict future cardiovascular events after an ACS. Several risk scores have been developed for risk assessment in ACS, including GRACE (Global Registry of Acute Coronary Events), SYNTAX, the TIMI risk score, all of which have been validated in predicting MACE rates.[63–65]

Our systematic analysis showed that several investigations have studied the correlation between EAT thickness and established ACS risk scores.[38,43–45] One study[43] found a significant association between EAT and GRACE scores ($p < 0.001$), though this was not corroborated by other studies.[38] The angiographic SYNTAX score for coronary lesion severity and the clinical TIMI risk score for adverse coronary events were also found to be significantly linked with EAT.[38,40,44] Being associated with ACS severity and risk prediction scores and connected with markers that express an increased patient vulnerability for acute coronary syndromes, at the same time being proven as an independent CAD,[53] EAT qualifies as a candidate for inclusion in current ACS risk scores.

One of the included studies hypothesized that an increased thickness of the epicardial fat is linked to impairment in the ST-segment resolution following revascularization in acute MI patients.[45] ST-segment resolution is a surrogate for tissue level reperfusion, illustrating the no-reflow phenomenon after primary PCI, and the lack of ST-segment regression after PCI has been proved to be a predictor for in-hospital mortality rates.[66,67]

EAT AND MAJOR ADVERSE CARDIOVASCULAR EVENTS

Epicardial fat might provide supplementary evidence regarding future cardiac events in patients with acute coronary syndromes. It is well known that an increased systemic inflammatory status leads to a poorer outcome in patients with STEMI.[68,69] Being an active metabolic tissue that secretes inflammatory cytokines and chemokines, epicardial fat could contribute to the overall inflammation, thus negatively impacting the outcome of ACS patients.4 EAT thickness can be used as a predictor of MACE, including MI and cardiovascular death.[70] Furthermore, an increased EF volume was shown to predict MI or cardiovascular death in patients suspected of CAD.[71] In a study that compared MACE individuals with event-free controls, patients with MACE had a significantly higher EF volume, even after multivariate adjustments for age, BMI, coronary calcium score, and Framingham risk score.[72]

The present review included two studies that evaluated the MACE rate with different endpoint evaluation times.[40,42] Wang *et al.* (2014) evaluated the influence of EAT thickness on the rate of major events during hospitalization, and after multivariate adjustments, concluded that the cut-off value for epicardial fat thickness (EFT) was 4.7 mm for predicting the primary endpoint (OR: 0.13, 95% CI: 1.05–1.62).[40] Tscharre *et al.* (2016) concluded that EFT was predictive for MACE rates during a follow-up period of three years (HR: 1.524, 95% CI: 1.0–2.2).[42]

EAT — ECHOCARDIOGRAPHY VERSUS CARDIAC CT

EAT, appraised by echocardiography, was shown to be associated with the EFV assessed by CT.[25,26] While cardiac CT and MRI allow the volumetric assessment of endocardial adipose tissue, echocardiography determines only the regional thickness of EAT. Since a close relationship has been shown to exist between EAT volume and thickness, echocardiographic measurement of EAT is preferable due to low costs, high availability and reproducibility, noninvasiveness, and no exposure to radiation.[73]

STUDY LIMITATIONS

Although initially we sought to conduct a systematic review of studies that assessed EAT using echocardiography in comparison with cardiac CT, in the course of our search we found that there were few studies that used CT in emergency clinical settings for diagnosing and managing acute coronary syndromes.

Secondly, cut-off values for epicardial fat have not been reproduced, due mainly to the fact that there are assorted descriptions of EF aggregation reported in the literature.

The power of this systematic review, in common with similar studies, is limited by the quality of the incorporated manuscripts, the study designs, and the statistical methods that had been used.

Regardless of these limitations, we are of the opinion that the study provides insights into the role of EAT in diagnosing and managing patients with acute coronary syndromes.

CONCLUSIONS

Epicardial adipose tissue, evaluated either by thickness using echocardiography, or by volume using cardiac CT, is associated with the severity of coronary stenosis, with the clinical and angiographic risk scores for acute coronary syndromes, and also with indicators of coronary reperfusion. Information provided by epicardial fat tissue can be used as predictors of major cardiovascular events in patients with acute coronary syndromes, over both short and long term.

CONFLICT OF INTEREST

Nothing to declare.

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