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MINIREVIEWS

Epicardial adipose tissue in diabetic myocardial disorder: Role of echocardiography

Ana Đuzel Čokljat, Petra Grubić Rotkvić, Damir Čokljat, Jerko Ferri Certić, Zdravko Babić

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Ana Đuzel Čokljat, Damir Čokljat, Jerko Ferri Certić, Department of Internal Medicine, General Hospital Dubrovnik, Dubrovnik 20000, Croatia

Petra Grubić Rotkvić, Department of Cardiology, University Hospital Centre Zagreb, Zagreb 10000, Croatia

Zdravko Babić, Department of Cardiology, University Hospital Centre Sestre Milosrdnice, Zagreb 10000, Croatia

Co-corresponding authors: Ana Đuzel Čokljat and Petra Grubić Rotkvić.

Corresponding author: Ana Đuzel Čokljat, MD, Department of Internal Medicine, General Hospital Dubrovnik, Ulica dr. Roka Mišetića 2, Dubrovnik 20000, Croatia.
ana29.djuzel@gmail.com

Abstract

Epicardial adipose tissue (EAT) is an active form of visceral adipose tissue that can affect myocardial function due to shared circulation with the myocardium. Given its rapid metabolic activity, EAT is considered a potential therapeutic target for medications that modulate fat and is a potent marker of metabolic changes including those observed in diabetic cardiomyopathy. Recent investigations propose an association between EAT accumulation and chronic diseases such as type 2 diabetes mellitus (T2DM), atrial fibrillation, and heart failure with preserved ejection fraction. According to the method first described by Iacobellis *et al*, EAT thickness is identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, measured in the parasternal short- and long-axis views at end-systole using ultrasound. Ultrasound of EAT is a safe, cost-effective, and readily available tool for cardiometabolic risk assessment. This minireview investigates the current role of echocardiography in the assessment of EAT thickness in patients with T2DM, regardless of the presence of overt heart failure. We also discuss whether changes in EAT thickness may be used as a significant marker of disease progression and if delta EAT thickness could serve as a surrogate of effective therapy.

Key Words: Epicardial adipose tissue; Echocardiography; Type 2 diabetes; Heart failure; Diabetic myocardial disorder; Diabetic cardiomyopathy

Core Tip: Epicardial adipose tissue (EAT), as measured by two-dimensional echo, provides additional information for the assessment of diabetic myocardial disorder. It may serve as a novel tool for risk estimation of the progression from asymptomatic to symptomatic heart failure. Given its rapid metabolic activity, EAT may serve as a target for existing and emerging therapies. The proposed cardiovascular benefits of EAT lipolysis in the context of diabetes mellitus type 2 could help clarify the mechanisms underlying its therapeutic modulation. Excessive EAT can be regarded, *de facto*, as an indicator of diabetic pericardial disorder.

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INTRODUCTION

Epicardial adipose tissue (EAT) refers to a distinct form of visceral adipose tissue (VAT) that lies between the myocardium and visceral layer of the pericardium (epicardium). In the absence of a fascial layer between the EAT and myocardium, a common microcirculatory network supplies both structures[1]. The role of EAT remains ambiguous, as it can exhibit both a protective role through its thermogenic brown fat-like function or contribute to pathologic metabolic alterations with the occurrence of potentially detrimental effects *via* the endocrine, vasocrine, and paracrine secretion of proinflammatory and profibrotic cytokines[2]. Excessive EAT is strongly linked to heart failure with preserved ejection fraction (HFpEF), whereas its association with HF with reduced EF (HFrEF) is less clearly defined[3-6] leaving its precise role in HF syndrome unresolved. Obesity and chronic inflammation promote accumulation of EAT, initiating local inflammation, disrupted adipogenesis, and ultimately feeding back into systemic inflammation and creating a self-induced cycle[7]. Nevertheless, a meta-analysis investigating the influence of lifestyle changes on EAT thickness, including regular physical activity, restrictive diet, and bariatric surgery, has not produced in consistent results[8].

The increasing prevalence of type 2 diabetes mellitus (T2DM) in modern society has been associated to morbidity and mortality, largely due to accompanying cardiovascular disease (CVD) with HF being the leading cause[9]. A link between asymptomatic cardiac dysfunction and a higher risk of incident HF in patients with T2DM has been observed, even in the absence of coronary artery disease (CAD) or hypertension[10]. An analysis of two prospective cohort studies involving patients with T2DM demonstrated an incremental risk of adverse CV events including incident HF, associated with asymptomatic echocardiographic abnormalities, such as left ventricular hypertrophy, modest systolic dysfunction and impaired myocardial strain[11]. Furthermore, a study in individuals with T2DM and stage B HF reported that patients with T2DM had significantly higher EAT compared to patients without abnormal glycemic control, regardless of their body mass index (BMI)[12]. In addition, it was found that individuals with normal weight and T2DM had a significantly increased EAT, as well as a high prevalence of stage B HF comparable to overweight/obese T2DM individuals[12]. This study places strong emphasis on the significance of BMI in the context of obesity, a topic that will be explored further in the text. Future research should evaluate the hypothesis that excessive EAT in individuals with T2DM is a more accurate risk marker for developing overt HF and other CV complications than obesity as defined by BMI.

BASIC ANATOMY, PHYSIOLOGY, AND PATHOPHYSIOLOGY OF EAT

EAT is located between the myocardium and epicardium[13], nourished by the coronary artery branches. Unlike EAT, overlying pericardial adipose tissue is nourished by non-coronary arteries, and usually maintains its shape without significant deformation during diastole. Predominantly located in the atrioventricular groove and interventricular groove, EAT is further divided into myocardial EAT representing adipose tissue adjacent to myocardium and peri-coronary EAT, located around coronary artery adventitia[14]. Under physiological conditions, EAT acts as a buffer providing the myocardium with free fatty acids while simultaneously preventing excess fatty acids[15]. EAT has a unique transcriptome differing from subcutaneous adipose tissue and VAT at varied locations[16]. Genetic, epigenetic, and environmental factors can initiate a transition from a protective to a maladaptive response of EAT, promoting the proinflammatory and profibrotic phenotype.

Given its close anatomical proximity to the epicardial coronary arteries, thickened and dysfunctional EAT may contribute to the progression of atherosclerosis through paracrine and vasocrine signaling. An intriguing hypothesis suggests that thickened adipose tissue can lead to chronic hypoxia due to EAT accumulation where oxygen demand exceeds blood supply resulting in accelerated angiogenesis[17]. This process is seldom effective and results in further relative hypoxia of EAT. Relative hypoxia promotes proinflammatory cytokine release, migration of macrophages, and other immune cells towards EAT[17]. Adipose tissue hypoxia is also associated with a decrease in insulin sensitivity of adipocytes[17]. Notably, this pathophysiological transformation is not unique for EAT but is relevant to adipose tissue at different sites. However, EAT's unobstructed proximity to the heart and shared circulation may enhance the harmful effects of its pathological transformation. Resulting hypoxic, thickened, and inflamed EAT may start infiltrating and compressing the underlying myocardium, promoting diastolic dysfunction[18]. Furthermore, EAT may secrete

proinflammatory adipocytokines to the adjacent myocardium and release them directly into the myocardium and coronary arteries *via* the paracrine pathway[18,19]. On the other hand, the vasocrine signaling pathway hypothesis proposes that adipokines are not diffused directly into adjacent tissues but are released into the vasa vasorum and carried downstream[20]. To evaluate whether EAT can adapt to various metabolic conditions and resume its initial protective role, further investigations are needed. Basic physiological and pathophysiological EAT features are summarized in Table 1.

EAT IMAGING

The thickness of EAT can be measured using a standard two-dimensional (2D) echocardiography, as first described by Iacobellis *et al*[21], whereby EAT is identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. However, when inflammation or excess EAT is present, EAT can also be visible as the echo-dense space. EAT thickness is a marker of visceral adiposity and its variability (ranging from 1 mm to 25 mm) may reflect differences in intra-abdominal fat accumulation[22]. Excess visceral adiposity is characterized by increased visceral and ectopic fat deposition, adipocyte dysfunction, inflammatory and adipokine dysregulation, and insulin resistance[22]. The mechanisms by which an excess of VAT is related to various health outcomes are not fully understood and are under investigation. In addition, reduction in VAT or either fat depot should be expressed as a relative value rather than an absolute value. The wide range of EAT thickness reported in the literature is partly due to variability in measurement techniques. For this reason, as most authors suggest, we also suggest that all EAT measurements be performed at end-systole, the part of a cardiac cycle with maximum EAT thickness, to avoid variability in measurement techniques. Furthermore, we propose the use of ratios since EAT has shown a strong correlation with waist circumference and intracardiac fat, suggesting that the EAT-to-waist circumference ratio may serve as a more robust predictor of increased cardiometabolic risk than either measure on its own[22]. However, to date, no study has reported a reverse relationship between the delta waist circumference and corresponding delta EAT. Furthermore, the evident absence of established EAT reference ranges may be explained by the complex nature of cardiometabolic syndrome. For this reason, we propose routine ultrasound measurements of EAT thickness during initial and follow-up visits. Furthermore, we hypothesize that changes in EAT (delta EAT) may be more significant than absolute EAT thickness in CV risk assessment. Therefore, we recommend follow-up echocardiographic measurements for individuals with T2DM to gain more insight into the role of delta EAT.

At this stage, four different ultrasound 2D measurements of EAT thickness will be described as portrayed in Figure 1. The first measurement is obtained from the parasternal long-axis view. EAT thickness is measured perpendicularly to the free wall of the right ventricle at the end-systole, using the point perpendicular to the aortic annulus as the anatomical landmark[21] and the average value of three cardiac cycles at end-systole is then calculated. The second 2D measurement is obtained from the midventricular parasternal short-axis view, whereby EAT thickness is measured on the right ventricular free wall perpendicular to the interventricular septum at the mid-chordal level and the tip of the papillary muscles are used as anatomical landmarks. The average value of three cardiac cycles at the end-systole is then calculated.

The first two EAT thickness measurements taken from the parasternal long-axis and short-axis views are routinely performed using a phased-array (sector, cardiac) probe. By contrast, the third 2D measure of EAT thickness can be measured with a high-frequency linear probe (2.4-10 MHz). This measurement is taken in the anterior interventricular groove at the end-systole[23]. At this anatomical location, EAT thickness is measured from a modified three-chamber view after visualization of the distal left anterior descending (LAD) coronary artery and followed by further probe rotation to obtain a longitudinal section of LAD[23]. Following LAD visualization, EAT thickness is measured as the distance between the outer wall of the myocardium and the visceral layer of the pericardium, perpendicular to the pericardium[23]. The average value of three cardiac cycles at the end-systole is then calculated. The fourth 2D measure is obtained just to the right of the aortic annular plane where the greatest EAT thickness is expected due to the steep downward turn of the right ventricular free wall as it approaches the proximal ascending aorta (Rindfleisch fold)[24]. EAT is then visualized in a parasternal long-axis view at the level of the fold of Rindfleisch, between the free wall of the right ventricle and the anterior surface of the ascending aorta. After adequate visualization, the maximum EAT thickness is measured between the right ventricle wall and the visceral layer of the pericardium at the end-systole[24]. The average value of three cardiac cycles at the end-systole is then calculated. In a study by Parisi *et al*[24], EAT thickness was measured in 1050 individuals using a cardiac probe at the level of the Rindfleisch fold, a pericardial recess where the parietal pericardium does not exert a mechanical compression on VAT[25]. At this level, it is possible to directly visualize and measure the fat deposit between the visceral layer of the pericardium and myocardium. In this study[24], echocardiographic measurements were followed by two different cardiac magnetic resonance (CMR) measurements. The first CMR measurement was obtained in the parasternal long-axis view at the level of the Rindfleisch fold, corresponding to the site of echocardiographic EAT thickness assessment, and the second measurement was a volumetric CMR EAT measurement performed using standardized methods[24,26-29]. EAT thickness measured by echocardiography at the level of the Rindfleisch fold showed a good correlation with both EAT thickness and volume assessed by CMR. The correlation between echo-EAT thickness and CMR-EAT volume was statistically significant with a correlation coefficient equal to 0.61 (95%confidence interval [CI]: 0.44-0.74; $P < 0.001$), and echo-measured EAT thickness also showed a significant correlation with the CMR-EAT thickness, with a concordance correlation coefficient of 0.71 (95%CI: 0.54-0.82; $P < 0.001$) [24]. A separate study in 117 individuals with left ventricular EF (LVEF) > 40% showed a modest, but significant correlation between EAT on echocardiography and CMR[30] suggesting that echo measured EAT thickness may a be useful tool to investigate associations with CVD[30]. Furthermore, studies in patients without HF have shown an

Table 1 Role of epicardial adipose tissue

Physiologic	Pathophysiologic
Thermogenic brown fat-like function	Endocrine, paracrine, and vasocrine secretion of proinflammatory and profibrotic cytokines
Protective (*e.g.*, mechanical protection in the case of physical trauma)	Local inflammation, disrupted adipogenesis
Source of energy in case of metabolic demand	Acceleration of atherosclerosis
Storage compartment providing the myocardium with free fatty acids	Decreased insulin sensitivity of the adipocytes
Buffer preventing excess fatty acid influx	Ventricular dysfunction (Diabetic pericardial disorder)

association between EAT measured by CMR and echocardiography, where the echocardiographic measurement was taken over the right ventricle using standard views[21,31].

These results are important because CMR represents the gold standard for EAT assessment, but may not be routinely used for clinical purposes due to high costs and low availability, particularly for repeated measurements that are part of standard clinical follow-ups. An advantage of CMR imaging in comparison to echocardiography is an additional assessment of intramyocardial adiposity if magnetic resonance spectroscopy techniques are added[32].

Conversely, echocardiographic measurement of EAT offers several advantages including availability of the method, speed compared to other imaging methods, low-cost, ease of use, and reproducibility. Potential limitations include suboptimal acoustic windows, interobserver variability particularly in unexperienced investigators[30], and the lack of standardized reference values in the literature. An additional challenge is the heterogenicity in the timing of EAT measurement, as values are reported inconsistently, with some studies assessing EAT at the end-systole and others at the end-diastole, leading to unstructured and non-comparable data. To address this, we propose a uniform echo-EAT thickness measurement at the end-systole, when EAT reaches its maximum thickness. Furthermore, since EAT is a metabolically active adipose tissue with rapid metabolic turnover, we hypothesize that change in EAT thickness (delta EAT) is a more robust indicator of CV risk than absolute EAT thickness. Further studies are needed to test this hypothesis.

Another key limitation of echocardiographic EAT assessment is that it does not comprise peri-atrial or other volumetric measurements of EAT distribution. Nevertheless, these measurements can be performed both with CMR, and computed tomography (CT)[33,34]. This is important, as EAT volume is asymmetrically distributed around the heart and giving EAT location potentially greater relevance to HF than overall EAT volume[33]. In addition, CT also allows for assessment of EAT attenuation which has been associated with coronary inflammation[34]. Gorter *et al*[35] demonstrated that volumetric EAT quantification using cardiac CT is highly reproducible in comparison to simpler EAT thickness measurement and pericoronary fat thickness measurement, and that quantity of EAT and pericoronary fat is related to the presence of obesity and metabolic syndrome in patients suspected of CAD. Likewise, Gorter *et al*[35] also concluded that echocardiography can be used to assess EAT thickness as an easy and cost-effective alternative to cardiac CT. A systematic review and meta-analysis in individuals with low-to-intermediate CV risk showed that EAT volume, measured by CT, was independently associated with coronary artery stenosis, and myocardial ischemia[36]. An additional advantage of CT is its ability to evaluate EAT (and in general, VAT) density, which is linked to EAT inflammation and CAD[37]. Furthermore, cardiac CT allows for quantification of local fat components such as pericoronary adipose tissue and peri-atrial adipose tissue. On the other hand, echocardiographic EAT measurements at different sites [21-24] may help clarify different pathophysiological pathways through which EAT influences cardiac function.

Therefore, measurements of EAT at four different sites as described earlier in this text, may help clarify the specific role of excess EAT at each site. The regional distribution of EAT has an important role because each EAT depot may be anatomically and functionally different. Further investigations should examine whether pericoronary EAT thickness, measured in modified three-chamber view after visualization of LAD coronary artery, provides a stronger correlation with CAD than EAT thickness measured at other locations. Additionally, the specific regional distribution of EAT could imply different anatomic, functional, and genetic features, and this hypothesis should be further tested.

A potential limitation of CT-based EAT measurement is the historically inconsistent definition of EAT: One study defined it as adipose tissue inside the pericardial sac, corresponding to current definition, whereas others included tissue adjacent to the outer layer of the pericardial fat, now classified as pericardial adipose tissue[38,39]. In a population-based cohort study with over 32000 patient-years of follow-up, authors investigated the association between EAT volume measured by CT and incident myocardial infarction (MI), with resulting incidence of MI increasing fivefold from the first to fourth quartile of EAT volume. This finding suggests that excess EAT volume could serve as an early marker of subclinical atherosclerosis[40]. Despite evidence strongly associating CT-derived EAT volume with prevalent and incident CAD, its assessment is not part of routine clinical practice. This is likely due to challenges related to cost, time, CT availability, and the potential risks associated with repeated radiation exposure for follow-up imaging.

To conclude, although echocardiographic EAT assessment is not the gold standard method for EAT evaluation, it represents an affordable, widely available, safe, and reproducible method that correlates well with CMR and CT measurements. Thus, echo-measured EAT thickness may serve as a valid clinical surrogate for more complex imaging methods such as CMR and CT. The advantages and limitations of echo-EAT thickness measurement are summarized in Table 2.

Table 2 Advantages and limitations of echocardiographic (*i.e.*, ultrasound) epicardial adipose tissue thickness measurement

Advantages	Limitations
Non-invasive, easily done, cost-effective	No regional EAT measurement (*e.g.*, atrial EAT)
Very little time consuming	Interobserver variability (especially in unexperienced investigators)
Simultaneous assessment of cardiac function	Non-ideal acoustic window
Reproducible	The lack of a reference range
Readily available for frequent follow-up	No volumetric assessment
Direct measure of visceral adiposity (rather than anthropometric measure)	No assessment of intramyocardial adiposity
Non-harmful	No EAT attenuation assessment (*e.g.*, inflammation)

EAT: Epicardial adipose tissue.

ROLE OF EAT: MARKER OF INCREASED CV RISK

During the neonatal period, EAT exhibits brown fat-like characteristics, and limited responsiveness to external factors [41]. With aging, epicardial adipocytes become more susceptible to environmental, metabolic, and hemodynamic influences, which gradually change the function of EAT from thermogenesis to energy storage[41]. Brown fat-like activity in EAT decreases substantially with age. Chronic and long-term ischemic conditions, such as advanced stages of CAD, can also suppress the brown fat-like activity of EAT[41]. In contrast to these findings, one study suggested a beneficial role of EAT, serving as a heat source for the myocardium during ischemia or hypoxia[42]. Further studies are needed to clarify the complex role of EAT in thermogenesis and its function during unfavorable hemodynamic conditions.

Recent investigations suggest an association between EAT accumulation and symptomatic HF (namely HFpEF), T2DM, and AF[43]. Nevertheless, the exact mechanism of how EAT impacts HF progression is not fully clarified. However, the lack of an anatomical barrier permits crosstalk between EAT and the underlying myocardium[44]. EAT may also help in distinguishing between different HFpEF phenotypes, a cardinal consideration in this heterogenous clinical entity where most treatments have shown mostly modest or neutral effects to date, with the exception of sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs), which will be discussed later.

Clinical studies evaluating targeted pre-HF therapy in patients with preserved LVEF, *i.e.* patients with echo-determined abnormal myocardial deformation and/or elevated filling pressures, are lacking[45]. According to current practice, treatment is focused on the management of comorbidities, *i.e.* arterial hypertension, T2DM, and obesity, attempting to slow or even stop progression from asymptomatic left ventricular dysfunction to symptomatic HF[46]. Elevated systolic and diastolic heart pressures are the most prominent risk factors for progression to clinical HF[47].

Diabetes mellitus implies a predisposition to diabetic cardiomyopathy, a specific form of cardiomyopathy characterized by a myocardial fibrosis, cardiomyocyte hypertrophy, and apoptosis that develops independently of concomitant macrovascular and microvascular diabetic complications[48]. Its pathophysiology is multifactorial, closely related to inflammation and oxidative stress but remains poorly understood and no specific therapeutic guidelines have yet been established[48]. A contemporary pooled analysis of three cohort studies consisting of 10208 individuals with and without T2DM, but without known CVD including overt HF, revealed a high prevalence of echocardiographic structural and functional abnormalities among patients with T2DM[49]. Echocardiographic findings including left atrial enlargement, left ventricular hypertrophy, and diastolic dysfunction have been proposed as prognostically relevant for incident HF over a 5-year follow-up[49].

A study in asymptomatic, hypertensive patients without CAD, comparing CMR findings between those with and without T2DM, suggested that the T2DM group exhibited more severe left ventricular concentric hypertrophy, greater impairment of myocardial strain and increased interstitial fibrosis[50]. These adverse cardiac abnormalities were found in asymptomatic T2DM patients despite having similar left ventricular mass and blood pressure as patients with lone arterial hypertension, and were associated with a distinct proinflammatory and profibrotic biomarker profile[50]. Prevention of HF syndrome is a main concern in patients with T2DM, especially among those with asymptomatic cardiac structural/functional abnormalities, *i.e.* possibly early diabetic myocardial disorder, where evidence remains sparse. Current preventive strategies encompass lifestyle interventions, glycemic control, blood pressure control and use of medical therapies with favorable CV effects[51]. A recent document proposes a new paradigm for myocardial diabetic disorder, previously referred to as diabetic cardiomyopathy, as systolic and/or diastolic myocardial dysfunction in the presence of diabetes[51]. This new document emphasizes the need to prevent the progression of early diabetic myocardial disorder to overt HF. However, the exact strategies to achieve this goal, beyond existing measures, remain a challenge for future investigations.

A previous lack of an established definition of myocardial diabetic disorder has limited exploration of specific treatment options. Strategies targeting cardiac remodeling, inflammation, oxidative stress, and adverse cellular pathways should be explored since the mechanistic nature of this disorder is not yet fully understood.

Since excessive EAT is associated with HFpEF, although the association is less well defined and more complex in HFrEF, the exact mechanism of this interplay has been investigated. Two basic concepts of potential EAT involvement in HFpEF have been proposed. The first is related to infiltration of EAT into the adjacent myocardium, which disturbs

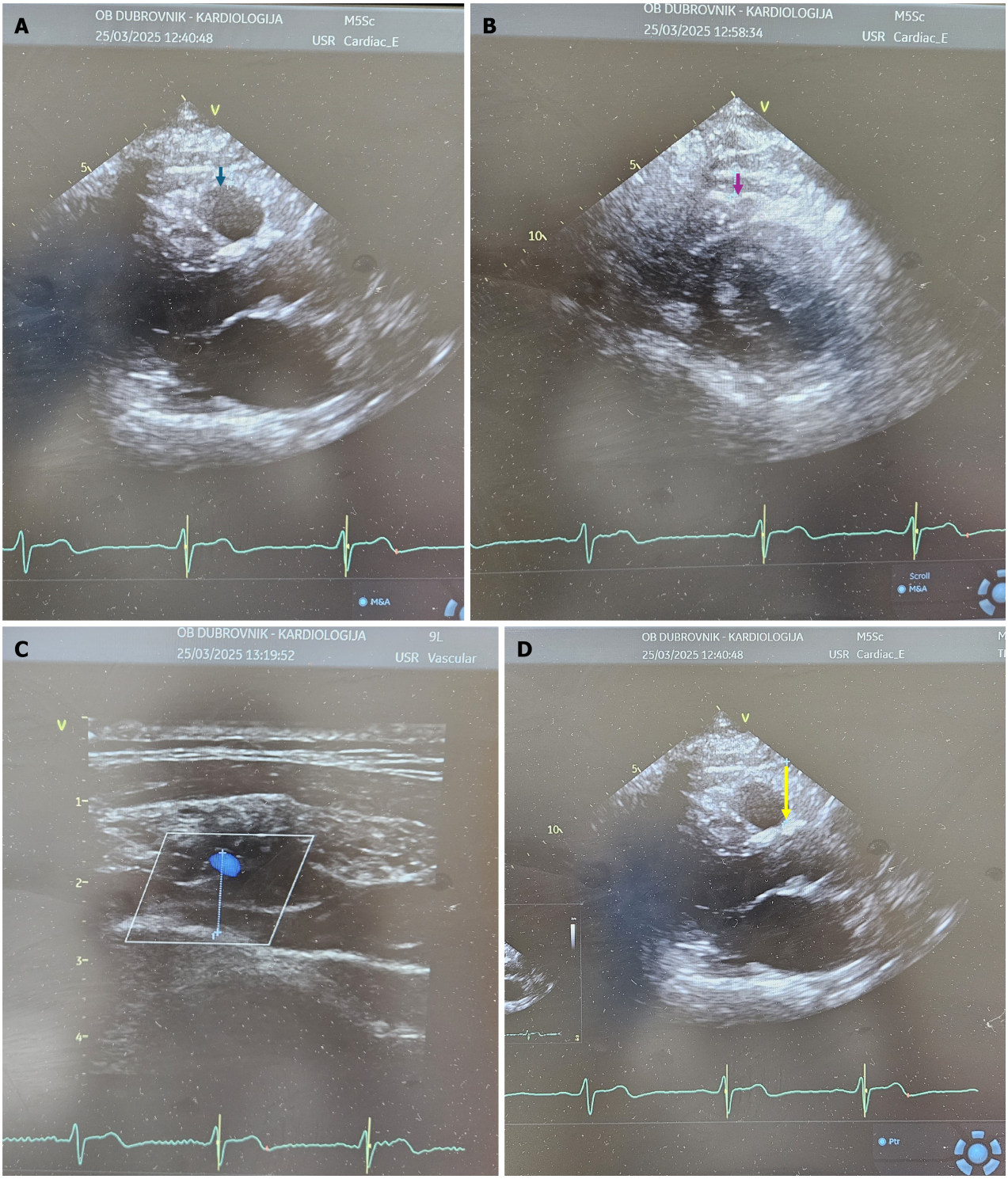

Figure 1 Epicardial adipose tissue thickness. A: Measured from parasternal long-axis view (blue arrow); B: Measured from parasternal short-axis view (purple arrow); C: Measured from modified three-chamber view with a linear probe (dotted line); D: Measured from parasternal long-axis view at Rindfleisch fold (yellow arrow).

myocardial architecture, stimulates myocardial thickening, and promotes diastolic dysfunction[18]. A study in patients undergoing aorto-coronary bypass surgery showed that EAT infiltrates adjacent atrial myocardium, affects atrial conduction and may trigger AF[18]. In addition, thickened and proinflammatory EAT secretes proinflammatory cytokines *via* paracrine and vasocrine secretion. A recent review article postulated a correlation between EAT infiltration into the myocardium and secretion of proinflammatory cytokines with incidence of ventricular tachyarrhythmia[52]. Nevertheless, the association between EAT infiltration into the myocardium and sudden cardiac death has yet to be fully clarified. The second mechanism of EAT involvement with HFpEF comprises a mechanical effect of thickened EAT analogous to that of a constrictive pericarditis[53]. Namely, if a pericardial dilatation is non-congruent with EAT expansion, *i.e.* pericardial restraint, the adjacent myocardium cannot further dilate in cases of demanding hemodynamic conditions due to limited pericardial pliability. Increased EAT volume, surrounded by a relatively stiff pericardial sac,

potentially constrains the myocardium, resulting in a diastolic dysfunction and elevated left ventricular filling pressure. Invasive hemodynamic testing in individuals with HFpEF and thickened EAT confirmed elevated left ventricular filling pressures and an increased left ventricular eccentricity index, indicating that increased left and right ventricular coupling, *i.e.* increased ventricular interdependence, is directly related to excessive EAT thickness due to pericardial constraint[53-55].

Excessive body adipose tissue causes oxidative damage, metabolic, inflammatory, hormonal, and hemodynamic disturbances that affect the heart and blood vessels[56,57]. Since most patients with T2DM are overweight/obese, a potential adverse mechanism of progression to higher stages of the HF continuum is enhanced ventricular interaction. As previously elaborated, chronic increases in heart volume and EAT may increase pericardial restraint and enhance ventricular interaction if the pericardium does not dilate as much as the heart volume expands, as observed in the obese HFpEF subjects[58]. Obesity-related HFpEF is an authentic form of HF and represents a clinically relevant phenotype that may require specific treatments[58]. Obesity-related HFpEF is the predominant form of HFpEF in patients with T2DM. Because EAT directly correlates with BMI[54], and EAT is a metabolically active tissue, it is likely that overweight/obese individuals are more exposed to cytokines released from EAT. Excessive, metabolically transformed EAT can have adverse effects on cardiac function. In addition to these endocrine effects, excessive EAT can lead to deleterious mechanical effects and may contribute to the increased intracardiac pressures in obese HFpEF individuals, particularly during exercise[58]. However, since previous studies have inconsistently demonstrated a correlation between EAT and BMI, further studies are warranted[8,12,54].

Further studies are required to determine whether interventions to reduce EAT might be beneficial in overweight/obese T2DM patients, as well as overweight/obese patients in general. These studies should aim to compare the benefits of reducing EAT with those of total body weight reduction. In addition, EAT may act as a marker of inflammation in T2DM individuals with a distinct proinflammatory and profibrotic biomarker profile[59-61], as well as in overweight/obese individuals.

Notably, since BMI does not reliably indicate visceral adiposity and the association between BMI and visceral fat has not been well explored in asymptomatic patients with T2DM, further studies are warranted for this group of patients. Detection of VAT, which is the fat deposit around the internal organs, represents a key point for identifying visceral obesity. Iacobellis *et al*[21] demonstrated that echo-measured EAT thickness showed a strong correlation with anthropometric and imaging VAT measurements. Echocardiographic measurements were performed on the free wall of the right ventricle, both from parasternal long- and short-axis views. In this study, linear regression analysis demonstrated an excellent correlation between EAT thickness and waist circumference (r = 0.895, P = 0.01) and magnetic resonance imaging (MRI) abdominal VAT (r = 0.864, P = 0.01). Multiple regression analysis indicated that EAT thickness (r^2 = 0.442, P = 0.02) was the strongest independent variable correlated to MRI VAT. The authors concluded that transthoracic echocardiography could be suitable as an easy and reliable imaging method for VAT prediction. In our opinion, these results are important in promoting EAT as a surrogate marker of visceral adiposity. These results suggest that transthoracic echocardiography may serve as useful imaging technique for VAT estimation, making echo measured EAT thickness applicable across a wider spectrum of metabolic syndrome.

The intriguing concept of "pleiotropic'" effect of certain antidiabetic and cardiometabolic medications may also involve the reduction of EAT, as will be discussed further bellow. To conclude, EAT is a marker and a possible target of pathologically adipogenous metabolic and systemic inflammatory disorders, such as the altered metabolism observed in patients with T2DM. Because of its functional proximity to the myocardium, EAT has been suggested to have a role in the progression and development of leading causes of morbidity and mortality such as CAD, AF, and HFpEF. Studies that explore association of EAT accumulation with CVD using different imaging methods are summarized in Table 3.

ROLE OF EAT: TARGET OF CARDIOMETABOLIC THERAPY

Since EAT contributes to the pathophysiology of T2DM[62,63], it may represent a promising therapeutic target in CV risk reduction. However, no treatments specifically targeting EAT metabolism and/or its reduction have been proven successful to date. Here we summarize medical therapies approved for T2DM that have demonstrated reductions in both EAT volume and its inflammatory properties, while also reducing CV risk.

Semaglutide, a GLP-1RA, has been revealed as an effective treatment for regulating both obesity and T2DM. In addition to providing sustained weight loss, recent evidence suggests a beneficial role in CV risk reduction in overweight/obese patients with pre-existing CVD without T2DM[64], as well as in improving symptoms and functional status in obesity-related HFpEF and T2DM[65]. Particularly, human EAT expresses the GLP-1R, a feature that is not attributable to subcutaneous fat[66]. EAT was obtained from subjects with T2DM and CAD who were candidates for an elective coronary artery bypass graft surgery[66], making EAT a compelling target for pharmacological treatment. However, the exact mechanism behind the fat modulation in response to GLP-1R activation remains unclear. Activation of these receptors causes alteration of adipose tissue metabolism, and further studies are needed to clarify potential mechanisms (*e.g.*, enhanced fat utilization, favorable fat differentiation). Therefore, the presence of GLP1R in EAT supports the hypothesis of a direct effect on this distinctive adipose tissue depot. Clinical studies have confirmed the efficacy of GLP-1RA in reducing EAT volume or thickness up to 42% during a follow-up of 12-24 weeks[67-70].

A significant progress in HF prevention in T2DM occurred following the results of CV outcome trials with SGLT2 inhibitors, which have shown a consistent reduction of approximately 30% in the risk of HF hospitalization[71-74]. However, these trials were confined to patients with established atherosclerotic CVD or with multiple risk factors, and the efficacy of SGLT2 inhibitors in patients at lower CV risk is less clear[75]. Based on a large cohort study including

Table 3 Association of epicardial adipose tissue accumulation with cardiovascular disease (heart failure with preserved ejection fraction, coronary artery disease, atrial fibrillation)

Imaging method for EAT assessment	CVD and related references
ECHO	HFpEF[12,53,54,58], CAD[24,62], AF[52,91]
CT	HFpEF[6], CAD[34-40,89,93], AF[18,52,91,92]
CMR	HFpEF[32,33,43,59,88,90], CAD[24,32] AF[43,52,91]

AF: Atrial fibrillation; CAD: Coronary artery disease; CMR: Cardiac magnetic resonance; CVD: Cardiovascular disease; CT: Computed tomography; EAT: Epicardial adipose tissue; ECHO: Echocardiography; HFpEF: Heart failure with preserved ejection fraction.

309056 patients with T2DM predominantly without a CVD, which compared SGLT2 inhibitors with other glucose-lowering drugs[76] and found a lower risk of HF hospitalization and death in the SGLT2 inhibitors group, it is reasonable to hypothesize therapeutic benefits of SGLT2 inhibitors for patients with T2DM at lower risk[76]. A possible mechanism may be through the reduction of EAT thickness or volume, as shown with SGLT2 inhibitors dapagliflozin and empagliflozin[77-80]. Díaz-Rodríguez *et al*[80] found that the use of SGLT2 inhibitors was associated with an increase in EAT glucose uptake, reduced secretion of proinflammatory cytokines, and improved differentiation ability. Another study demonstrated that SGLT2 inhibitors improve not only EAT but also interstitial myocardial fibrosis, aortic stiffness, and inflammation markers in non-T2DM individuals with HFrEF[78]. A recent systematic review and meta-analysis of cardiometabolic drugs found that GLP-1RA are more effective than SGLT2 inhibitors in reducing EAT, while statins had a rather mild effect[81]. Meta-regression analysis revealed that the most effective treatment with these drugs could be achieved in a group of younger patients with high BMI[81]. This observation is especially relevant in early recognition of diabetic myocardial disorder and prevention of overt HF. Since glucose-lowering drugs, such as SGLT2 inhibitors and GLP-1RA, have cardioprotective effects independent of blood glucose-lowering, they could be considered pharmacological armor used to confront cardiometabolic disorders. Reduced EAT favorably affects HF, AF, and CAD burden, and prevents negative cardiac remodeling, resulting in CV risk reduction. More studies are required to identify therapeutic options that specifically reduce EAT accumulation and inflammation[82] to improve outcomes for patients with T2DM.

MEANING OF DELTA EAT: CLINICAL IMPLICATIONS

Diabetic myocardial disorder exemplifies increased, yet still modifiable risk for CV complications. While most patents with T2DM are overweight/obese, individuals with T2DM and normal weight, as defined by a BMI < 25 kg/m^2, may potentially have higher mortality than those who are overweight or obese[83]. However, unlike EAT, normal weight is not a direct measure of adiposity based on BMI. EAT is a marker of visceral adiposity, which represents a risk factor for the development of T2DM and CV complications attributed to adiposity[2,21,84,85]. The inability of BMI to reflect cardiometabolic risk is partly related to the fact that BMI alone is an insufficient biomarker of total body, and especially, central abdominal fat mass and does not account for the extreme variation in VAT distribution between individuals[85]. Conversely, EAT strongly correlates with waist circumference, intra-abdominal fat as well as intracardiac fat and serves as a marker of visceral adiposity[21,85]. Obesity represents a risk factor for HF and multisystem changes that comprise the "heart-adipose tissue axis" with bidirectional effect: Fatty acid metabolites affect myocardial metabolism and function, while cardiac peptides affect fatty acid availability[86]. Obesity, defined as a BMI > 30 kg/m^2, is an important factor in the development of HFpEF, however, BMI poorly correlates with visceral adiposity, a more relevant feature of obesity[87]. Excessive EAT thickness predicts a poorer prognosis, independently of BMI[88]. Furthermore, data on EAT thickness measured by echocardiography confirmed an association of EAT with BMI in HFpEF patients[53]. On the other hand, the role of EAT volume in predicting the early stages of atherosclerosis in asymptomatic individuals was often independent of obesity[89]. Further investigations are warranted to identify different specific groups of patients in the trajectory of the EAT-BMI correlation, since the obesity paradox is of great importance for individuals with T2DM. Nevertheless, excessive EAT correlates with HF[43,90], AF[91,92], and CAD[36,37,93]. Considering EAT can contribute to local insulin resistance in coronary arteries among patients with T2DM[62], and since T2DM is a major trigger for EAT inflammation [82], the resulting increased atherogenicity of EAT in patients with T2DM makes EAT a very interesting choice for future investigations.

Adipose tissue surrounding coronary arteries may contribute to the development of coronary atherosclerosis given its localization and potential for local production of inflammatory cytokines[35]. The role of inflammatory cytokines has been studied mostly in animal models. Briefly, a study in experimental pigs with CAD demonstrated that aerobic exercise training reduced the inflammatory response in myocardial EAT but not in peri-coronary EAT[14]. Furthermore, a mouse model of visceral-like cardiac fat with expression of a key modulator of local insulin-like growth factor bioavailability with likely paracrine effects was established to support future mechanistic studies of cardiac adipose tissue[94]. EAT in rodents is normally located in the atrial–ventricular groove that is derived from the epicardium[95]. These findings on experimental animals are important because human EAT is usually obtained during cardiac surgery[18,96], where most patients suffer from CAD which can be a confounding factor. Therefore, a study in experimental healthy animal models and animal models with T2DM should be conducted to further explore metabolic properties of EAT.

A meta-analysis of 13 studies (n = 1102 patients), where EAT thickness was measured by echocardiography in 11 studies, and the EAT volume was measured by CT in 2 studies, concluded that T2DM individuals have a significantly higher amount of EAT compared with non-T2DM individuals[97]. These results emphasize clinical significance of EAT measurement, particularly for more precise risk-assessment among individuals with T2DM.

Therefore, it is reasonable to include EAT assessment in everyday practice for T2DM patients. Furthermore, EAT thickness should be included in future risk-scores, markedly for patients with T2DM where excessive EAT may compromise hemodynamic and metabolic homeostasis. Finally, EAT should be included in assessment of therapy effectiveness to clarify clinical, hemodynamic, and biochemical implications of EAT reduction.

CONCLUSION

The prevention of clinical HF remains a major challenge in treatment of patients with T2DM. Among this population, patients with asymptomatic cardiac structural/functional abnormalities represent a group with the greatest potential to benefit from early treatment. Considering the distinctive property of EAT having a shared microcirculation with the underlying myocardium, excessive EAT may serve as a marker of diabetic pericardial disorder with corresponding metabolic and hemodynamic implications.

EAT is a modifiable risk factor that can be regularly assessed during routine echocardiographic examination and thereby is of value in risk stratification. Echocardiographic assessment of EAT is a readily available, easily performed, cost-effective and non-invasive method. 2D ultrasound measurements have shown good correlation with CMR and CT; however, a standardized EAT echo-algorithm is needed and should be introduced into guidelines and followed routinely in clinical practice.

In this paper, we described in detail four different sites for echo-EAT measurement with potentially different clinical implications. Examining EAT distribution and relative changes in its thickness (delta EAT) as a follow-up, instead of examining absolute EAT thickness may be beneficial in evaluating evolution of myocardial diabetic disorder and clinical response to therapy. EAT could thus serve as a useful marker for risk assessment in T2DM individuals, as well as a potential target for contemporary and novel medical therapy. Given that patients with T2DM manifest excess EAT in comparison to non-T2DM individuals, further investigations are warranted to provide clarity on modes and implications of the interplay between diabetic myocardial disorder, formerly known as diabetic cardiomyopathy, and diabetic pericardial disorder embodied by EAT.

We propose a new syntagma "diabetic pericardial disorder", which includes both unfavorable metabolic and hemodynamic effects of EAT with resulting primarily diastolic left ventricular dysfunction. Diabetic pericardial disorder contributes to a higher risk of incident HF in patients with T2DM.

FOOTNOTES

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Country of origin: Croatia

ORCID number: Ana Đuzel Čokljat 0000-0003-0095-2987; Petra Grubić Rotkvić 0000-0002-2587-1932; Damir Čokljat 0009-0008-3221-7534; Jerko Ferri Certić 0000-0002-0136-7184; Zdravko Babić 0000-0002-7060-8375.

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