Epicardial adipose tissue: an emerging biomarker of cardiovascular complications in type 2 diabetes?

Regitse Højgaard Christensen, Bernt Johan von Scholten, Louise Lang Lehrskov, Peter Rossing and Peter Godsk Jørgensen

Abstract: Type 2 diabetes (T2D) is associated with an increased risk of cardiovascular disease and heart failure, which highlights the need for improved understanding of factors contributing to the pathophysiology of these complications as they are the leading cause of mortality in T2D. Patients with T2D have high levels of epicardial adipose tissue (EAT). EAT is known to secrete inflammatory factors, lipid metabolites, and has been proposed to apply mechanical stress on the cardiac muscle that may accelerate atherosclerosis, cardiac remodeling, and heart failure. High levels of EAT in patients with T2D have been associated with atherosclerosis, diastolic dysfunction, and incident cardiovascular events, and this fat depot has been suggested as an important link coupling diabetes, obesity, and cardiovascular disease. Despite this, the predictive potential of EAT in general, and in patients with diabetes, is yet to be established, and, up until now, the clinical relevance of EAT is therefore limited. Should this link be established, importantly, studies show that this fat depot can be modified both by pharmacological and lifestyle interventions. In this review, we first introduce the role of adipose tissue in T2D and present mechanisms involved in the pathophysiology of EAT and pericardial adipose tissue (PAT) in general, and in patients with T2D. Next, we summarize the evidence that these fat depots are elevated in patients with T2D, and discuss whether they might drive the high cardiometabolic risk in patients with T2D. Finally, we discuss the clinical potential of cardiac adipose tissues, address means to target this depot, and briefly touch upon underlying mechanisms and future research questions.

Keywords: epicardial adipose tissue, type 2 diabetes, cardiovascular disease, cardiac adipose tissue, pericardial adipose tissue

Introduction

Diabetes is one of the fastest-growing health challenges, with 463 million diagnosed today and rising to an estimated 700 million by 2045. Type 2 diabetes (T2D) is by far the most prevalent subtype, accounting for 90% of all cases of diabetes. Patients with T2D have 2- to 4-fold increased risk of cardiovascular disease (CVD) and heart failure, and, in 2019, more than 4 million people died globally from diabetes-related complications, namely CVD and heart failure. In order to prevent these premature deaths, there is a need for improved understanding of the pathophysiology, and thereby identification, of novel risk factors that can aid early detection of high-risk patients and aggressive treatments.

Obesity is one of the important risk factors driving the increased rate of CVD and heart failure in T2D due to, for example, altered hemodynamic load, neurohumoral activation, cardiac metabolism, adipokine secretion, and low-grade inflammation. Traditionally, obesity [defined as body mass index (BMI) > 30 kg/m²] per se has been viewed as a risk factor, but it is now recognized that fat depots are heterogenous; they differ
in their lipolytic activity, insulin sensitivity, secretory capacity and location, and, thus, in their atherogenic potential.15,16,18,20–24 This recognition has shaped the idea that it is primarily the visceral fat tissues located adjacent to the coronary arteries and the myocardium, the epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT), that accelerate coronary atherosclerosis and myocardial dysfunction due to their lipolytic and secretory hyperactivity leading to accumulation of toxic lipid metabolites in the myocardium and endothelium. Since T2D is accompanied by an expansion of EAT and PAT,25 these depots have been suggested to play a critical role in accelerating CVD and heart failure, particularly in patients with T2D.26–30 In support of this, high levels of EAT in T2D have been associated with atherosclerosis,31 diastolic dysfunction,32 and incident cardiovascular events.33

In this review, we outline the evidence that EAT acts as a link coupling diabetes and CVD. First, we present the pathophysiological mechanisms of EAT and PAT. Next, we account for the role of EAT in T2D, and, finally, we discuss the clinical potential of EAT in cardiovascular risk assessment and prevention, including how it can be targeted, and highlight future research questions.

Mechanisms of epicardial adipose tissue and cardiovascular pathophysiology

Anatomical characteristics of EAT affecting pathophysiology

Human EAT comprises adipocytes, stroma-vascular cells, neurons, and immune cells.34–36 Several characteristics related to the anatomy of EAT suggest that this depot may play a particularly important role in T2D and cardiovascular physiology and pathophysiology. First, since no fascia separates the tissues, EAT is in direct contact with the myocardium, allowing direct communication.37–39 Second, EAT and the myocardium share microcirculation, enabling vasocrine crosstalk.34,35,40 Third, despite the fact that EAT is associated mostly with the free wall of the right ventricle, the atrioventricular grooves, the apex, and the coronary arteries, it can cover up to 80% of the surface of the heart.34,41 Consequently, it is possible that EAT affects the circulation of the coronary artery and the myocardial diastolic and systolic properties mechanically.

Metabolic characteristics of EAT

For the major part of the 20th century, EAT was considered an unimportant inert supporting structure and energy depot of the heart, and attracted no attention apart from sporadic scientific papers that hinted at an active metabolic role.42 However, in 1989, Marchington et al. showed that lipolysis and fatty acid synthesis are greater in EAT compared with visceral fat (VAT) and other cardiac fat tissue (the PAT).41 This finding demonstrated that EAT is metabolically very active, which fitted with the finding that EAT adipocytes are smaller than other VAT cells.34 The appreciation of EAT as a metabolically active tissue motivated hypotheses of EAT being an important source of energy for the myocardium during periods of increased energy demand, and for being able to regulate free fatty acids levels in the coronary arteries and the accumulation of toxic lipid levels in cardiomyocytes.41

Later observational studies showed that the amount of EAT is increased in patients with T2D and CVD,25 and associated with intramyocardial fat accumulation.43–46 Translational mechanistic studies have shown that factors secreted from EAT disrupt fatty acid beta oxidation in cardiomyocytes, which normally is their major source of energy, accounting for 60–70% of the ATP produced.47 Thus, EAT is now recognized as a metabolic tissue, having the highest rates of lipolysis among the VAT depots, which, in obesity and T2D, may accelerate atherosclerosis in the coronary vasculature and lipotoxicity of the cardiomyocyte. Specifically for patients with T2D, it was found that the fatty acid profile of EAT was different from that of patients without T2D, and there was a decrease in 16:0 and omega 3 fatty acids and an increase of trans and conjugated fatty acids, which may worsen the formation of atheroma in the neighboring arteries.48 Secretory products from EAT from patients with T2D have also been shown to impair cardiomyocyte contractile function and fat oxidation.49 Overall, this metabolic hyperactivity indicates that EAT has a pathophysiological potential that may be aggravated by diabetes (Figure 1).

Adipokine secretion of EAT

The recognition of EAT as an active secretory tissue came from a seminal finding by Mazurek and colleagues in 2004.28 They showed that, in patients with coronary artery disease (CAD), EAT has a higher...
expression of pro-inflammatory cytokines (TNFα, IL-6, IL-1β, and others), a higher infiltration of chronic inflammatory cells, and secretes more pro-inflammatory cytokines compared with subcutaneous fat (SAT) biopsies from the same patient. Moreover, adiponectin expression was found to be lower in EAT from patients with CAD compared with non-CAD patients, and was lower in EAT compared with SAT. Chatterjee et al. expanded the adipokine list by demonstrating that cultured EAT adipocytes secrete IL-8. Subsequently, we found an indication that the local inflammatory response identified from the above studies could be measured systemically since EAT was associated with increased levels of IL-8 in plasma. However, whether EAT contributes markedly to the systemic low-grade inflammation needs to be investigated. Since then, others have confirmed the pro-inflammatory transcriptome of EAT, and indicated that EAT is more inflamed compared with intra-abdominal VAT. In patients with CAD, the secretome of EAT compared with SAT (in conditioned media from tissue explants) showed an atherogenic and inflammatory protein secretion profile. Moreover, a few studies have shown that the secretome of EAT disrupts cardiomyocyte metabolism, depresses cardiomyocyte contractile function, and alters expression of adhesion markers of primary cardiac endothelial cells. A recent intervention study in a rat model of myocardial infarction (MI) showed that surgical removal of EAT improves myocardial function following MI.
Causal evidence was further provided in a pig model of atherosclerosis, where resection of EAT from the anterior descending coronary artery reduced atherosclerotic plaque progression exclusively at the site of adipectomy. Obese mice fed a high fat diet specifically induced a pro-inflammatory adipokine state and increased adipocyte size in pericardial fat. Specific for T2D, a study by Sacks et al. indicated a predominantly pro-inflammatory adipokine signature in EAT from patients with metabolic syndrome and T2D, and this was confirmed by another research group who demonstrated that adiponectin gene expression was reduced, whereas CD68, MCP-1, and adipocyte size were increased in EAT from patients with T2D versus controls. The immune cell population found in EAT may also be influenced by diabetes since dendritic cells (professional antigen-presenting cells contributing to regulation of lymphocyte immune response) were downregulated, whereas infiltrating pro-inflammatory macrophages were upregulated in EAT from patients with T2D. Thus, EAT in T2D is particularly inflamed, which could accelerate atherosclerosis and cardiac complications in this population (Figure 1).

**Thermogenic capacity of EAT**

EAT is hypothesized to offer cardiac cryoprotection due to its thermogenic capacity, resembling that of brown/beige adipocytes. However, it is not known whether the thermogenic properties are functional in adult humans. Moreover, the heat generated by EAT thermogenesis may be of little or no physiological significance compared with the heat generated by the cardiomyocyte during the contractile cycle. Interestingly, a brown-to-white transition of EAT, due to downregulation of brown adipose tissue and upregulation of white adipose tissue associated genes, has been suggested to occur in patients with CAD compared with non-CAD. While it is not known whether T2D induces brown-to-white transition in EAT, or if this plays a role in mediating the cardiometabolic disease progression, a study by Moreno-Santos et al. supports this idea by showing that T2D was associated with decreased expression of PGC1α and UCP1 mRNA in EAT of patients with T2D and CAD, likely reflecting a loss of brown-like fat features (Figure 1).

**PAT pathophysiology**

Human PAT is located within, and on the external site of, the pericardium and is of a different origin (primitive thoracic mesenchyme) than EAT (splanchnopleuric mesoderm). PAT is supplied by blood from the thoracic vasculature and it is not in direct contact with the myocardium. Therefore, cardiac physiology may only be affected indirectly by PAT and it is also not directly affected by the “inside-to-out” paracrine signaling of the myocardium to the adipose tissue. Despite these marked differences of the depots, EAT and PAT have similar transcriptional profiles, and, when EAT and PAT are combined, this entire fat pad remains associated with an increased risk of future CVD, which has been shown in prospective studies. Similar to EAT, PAT has a higher expression of pro-inflammatory adipokines compared with intraabdominal VAT. While one paper suggests PAT to be more closely associated with cardiovascular risk factors compared with EAT, others have found that PAT alone does not predict future CVD and all-cause mortality in patients with diabetes. Overall, the literature points towards a role of PAT in cardiac disease pathology, but the physiology of PAT and its importance in cardiac disease progression in patients with T2D is not fully clarified.

Altogether, these mechanistic in vitro and in vivo studies indicate a pro-inflammatory, proatherogenic, and cardiotoxic effect of EAT and PAT in general and in diabetes. However, an important limitation is that, in all studies, the fat is obtained from patients/animals with established CVD undergoing open heart surgery, which per se affects the physiology of EAT and PAT and limits the conclusions. In the next section, we move from mechanistic to epidemiological and clinical studies investigating whether EAT plays a particularly important role for CVD progression in T2D.

**High levels of EAT in patients with T2D**

Several studies have reported that patients with T2D have higher levels of EAT compared with non-diabetic controls (Table 1). In 2009, Wang and colleagues showed that mean EAT was 166.1 ± 60.6 cm³ in patients with T2D compared with 123.4 ± 41.8 cm³ in patients without diabetes. This finding of high amounts of EAT in patients with T2D was confirmed by several subsequent studies, including a recent large cohort of 1000 patients. In 2014, a meta-analysis confirmed the association of EAT and parameters of the metabolic syndrome, and, in 2019, a
Table 1. Amount of EAT in patients with and without diabetes.

| Study                  | DM | Epicardial adipose tissue | Number (T2D versus controls) | Measurement tool | Year published |
|------------------------|----|---------------------------|------------------------------|------------------|----------------|
| Iacobellis et al.⁹⁰    | T1 | 7.2 ± 2.1 mm              | 4.9 ± 2.5 mm                 | 30 (15 versus 15) | Echocardiography | 2014           |
| Chambers et al.⁹¹      | T1 | 1.65 ± 0.44 mm            | 1.37 ± 0.27 mm               | 40 (20 versus 20) | Echocardiography | 2019           |
| Cetin et al.⁸⁸         | T2 | 6.0 ± 1.5 mm              | 4.4 ± 1.0 mm                 | 139 (99 versus 40) | Echocardiography | 2013           |
| Kang et al.⁹⁵          | T2 | 5.4 (4.2, 7.4) mm         | 3.9 (2.9, 4.8) mm            | 321 (40 versus 281) | Echocardiography | 2018           |
| Christensen et al.³²   | T2 | 4.6 ± 1.8 mm              | 3.4 ± 1.2 mm                 | 1004 (770 versus 234) | Echocardiography | 2019           |
| Ojeda-Peña et al.⁹⁶    | T2 | 7.0 mm³                   | 5.7 mm³                      | 60 (30 versus 30)  | Echocardiography | 2016           |
| Vasques et al.⁹⁷       | T2 | 10.2 ± 2.8 mm             | 8.2 ± 1.8 mm                 | 49 (31 versus 18)  | Echocardiography | 2015           |
| Peraza-Zaldívar et al.⁹⁸| T2 | 8 [7, 9] mm#              | 6 [2, 10] mm#               | 40 (22 versus 18)  | Echocardiography | 2016           |
| Seker et al.⁹⁹         | T2 | 6.5 ± 0.7 mm              | 5.3 ± 1.0 mm                 | 454 (186 versus 268) | Echocardiography | 2017           |
| Chun et al.¹⁰⁰         | T2 | 17.6 ± 6.7 mm             | 14.4 ± 5.9 mm                | 1048 (141 versus 907) | CT             | 2015           |
| Wang et al.¹⁰¹         | T2 | 5.0 ± 1.2 mm              | 3.1 ± 0.8 mm                 | 100 (68 versus 32)  | Echocardiography | 2017           |
| Yazici et al.¹⁰²        | T1 | 3.3 ± 1.1 mm              | 2.3 ± 0.3 mm                 | 79 (36 versus 43)  | Echocardiography | 2011           |
| Tonbul et al.⁸⁶        | n/a| 215.5 (126.5, 271.2) cm³  | 116.0 (91.6–139.4) cm³       | 60 (17 versus 43)  | CT             | 2011           |
| Versteylen et al.¹⁰³    | T2 | 98 ± 41 cm³               | 75 ± 34 cm³                  | 292 (83 versus 209) | CT             | 2012           |
| Wang et al.⁸⁵          | T2 | 166.1 ± 60.6 cm³          | 123.4 ± 41.8 cm³            | 127 (49 versus 78)  | CT             | 2009           |
| Milanese et al.¹⁰⁴      | T2 | 112.9 [21.4, 442.2] ml    | 82.6 [11.3, 318] ml          | 596 (215 versus 381) | CT             | 2019           |
| Svanteson et al.¹³      | T1 | 52.3 [36.1–65.5] cm³³     | 55 [38.3–79.6] cm³³a         | 148 (88 versus 60)  | CT             | 2019           |
| Zobel et al.¹⁰⁵         | T1 | 106 ± 78 ml               | 99 ± 61 ml³³b               | 90 (60 versus 30)  | CT             | 2020           |
| Zobel et al.¹⁰⁵         | T2 | 228 ± 97 ml               | 99 ± 61 ml³³b               | 90 (60 versus 30)  | CT             | 2020           |
| Yang et al.⁸²           | T2 | 89 ± 24.6 ml              | 67.6 ± 26.7 ml              | 407 (50 versus 357) | CT             | 2013           |
| Akyürek et al.¹⁰⁶       | T2 | 172.8 ± 64.9 cm³³         | 68.9 ± 37.7 cm³³            | 152 (90 versus 62)  | CT             | 2015           |
| Gaborit et al.¹⁰⁷       | T2 | 213 ± 34 ml               | 141 ± 18 ml                 | 30 (13 versus 17)  | MR             | 2012           |
| Rado et al.¹⁰⁷          | T2 | 7.7 [5, 10] cm³³x         | 10.3 [7, 14] cm³³x          | 272 (52 versus 220) | MR             | 2019           |
| van Woerden et al.¹⁰⁸   | T2 | 116 ± 10 ml/m³³           | 100 ± 10 ml/m³³             | 64 (28 versus 36)  | MR             | 2018           |
| Gullaksen et al.¹⁰⁹     | T2 | 119 ± 49 mm³              | 86 ± 40 mm³                 | 103 (44 versus 59)  | CT             | 2019           |

IQR (range).
⁶No SD or IQR available.
⁷Estimated or partly estimated from a figure.
⁺Not significant.
⁺⁺No discrimination between EAT and PAT.
CT, computed tomography; EAT, epicardial adipose tissue; IQR, interquartile range; MR, magnetic resonance; PAT, pericardial adipose tissue; SD, standard deviation; T2D, type 2 diabetes; T1D, type 1 diabetes.
meta-analysis including 13 studies confirmed the association of EAT and T2DM.25 While it is now clear that EAT is increased in patients with T2D, it is not established in type 1 diabetes (T1D). Although some studies do support a role of EAT in cardiac disease in T1D,90–92 it has recently been reported that EAT volume was not higher and not associated with coronary atherosclerosis in T1D patients.93 In support of this, we recently found patients with T1D to have lower cardiac adipose tissue volumes compared with patients with T2D, and levels similar to those of controls.94

Taken together, while not yet established in T1D, EAT is increased in patients with T2D, suggesting a potential importance in CVD progression in this population, which will be discussed below.

### Does EAT drive the association of T2D and CVD?

While several large-scale epidemiological studies,79,80,110–116 including recent meta-analyses,117,118 have implicated a role of EAT in provoking atherosclerosis independently of diabetes, the increased level of EAT in T2D may suggest it is an important link coupling diabetes and cardiovascular disease (Table 2). Wang and colleagues were among the first to describe an association of EAT volume with coronary artery calcium (CAC) scores and significant coronary lesions (more than 50% stenosis) in asymptomatic patients with T2D.85 Others have reported similar findings31,119 including Kim et al., who found an association with coronary lesions, but, on the contrary, reported that EAT was not independently associated with silent myocardial ischemia based on first-pass myocardial perfusion magnetic resonance (MR) images acquired during adenosine stress and at rest.120 Other cross-sectional studies have also reported that EAT in T2D is not associated with myocardial perfusion or microvascular dysfunction, which raise uncertainty of the functional importance of EAT in T2D.105,121 Nevertheless, an early prospective study by Yerramasu et al. found that EAT volume was an independent marker for the presence and severity of coronary calcium burden in 333 asymptomatic patients with T2D without prior history of CVD, and was associated with progression of CAC, whereas traditional measures of obesity were not independently associated with these endpoints.122 Other prospective studies have emerged since then, including a study by our group performed in a cohort of 200 patients with T2D.31 In this latter study, high cardiac adipose tissue levels (EAT+PAT) were independently associated with increased risk of incident CVD or all-cause mortality after 6.1 years of follow up. We confirmed this finding in a larger prospective study of 1030 patients with T2D, where the results additionally indicated a gender-specific role of EAT as its predictive potential for CVD was increased for men compared with women after 4.7 years of follow up.33 We also found that EAT modestly improved risk prediction when added to a model including traditional CVD risk parameters.

### Table 2. Association of EAT and CVD in T2D.

| Study                  | Association of EAT with                              | Design       | Year |
|------------------------|------------------------------------------------------|--------------|------|
| Wang et al.85          | CAC score, coronary lesions                          | Cross sectional | 2009 |
| Kazlauskaite et al.123 | Diastolic dysfunction                                | Cross sectional | 2010 |
| Yerramasu et al.122    | CAC score, CAC progression                           | Prospective  | 2012 |
| Versteylen et al.103   | Coronary artery disease                              | Cross sectional | 2012 |
| Kim et al.120          | Significant coronary stenosis, myocardial ischemia   | Cross sectional | 2012 |
| Chen et al.121         | Myocardial microvascular dysfunction^a              | Cross sectional | 2014 |
| Levelt et al.124       | Cardiac contractile dysfunction (impaired systolic and diastolic strain rates) | Cross sectional | 2016 |
| Uygur et al.125        | Coronary atherosclerosis                             | Cross sectional | 2017 |
| Christensen et al.31   | CAC score, incident cardiovascular events and all-cause mortality^b | Prospective  | 2017 |
| Reinhard et al.119     | CAC score                                            | Cross sectional | 2019 |
| Christensen et al.32   | Reduced diastolic function                           | Cross sectional | 2019 |
| Christensen et al.33   | Incident cardiovascular events and all-cause mortality | Prospective  | 2019 |

CAC, coronary artery calcium; CVD, cardiovascular disease; EAT, epicardial adipose tissue; PAT, pericardial adipose tissue; T2D, type 2 diabetes.

^aNot significant.

^bTotal cardiac fat (EAT+PAT).
Overall, whereas the main body of evidence suggests a role for EAT in the development of CVD in T2D, EAT is a heterogenous fat depot and may have different atherogenic potential depending on its location. Uygur et al. have suggested that the left atrioventricular groove EAT volume was superior in the prediction of CAD in patients with T2D without CAD history,¹²⁵ and Maimaituxun et al. identified that the local fat thickness surrounding the left anterior descending artery (LAD), when compared with EAT at other locations, was a useful surrogate marker for estimating the presence, severity, and extent of CAD, independent of classical cardiovascular risk factors.¹²⁶ A post hoc analysis from the CRISP CT study identified that the perivascular (epicardial) fat attenuation index (which captures coronary inflammatory load) at both LAD and the right coronary artery were predictive of all-cause and cardiac mortality and improved risk prediction algorithms in a mixed population of patients with and without T2D.¹²⁷ This finding suggests that the physiological state of EAT or PAT (e.g. inflammatory or brown-fat activity) compared with the amount may be a better estimate for the risk of CVD.

Regarding cardiac function, several studies have shown that EAT is associated with diastolic dysfunction.⁸⁸,¹²⁸–¹³⁴ Levelt et al. showed that lean versus obese patients with T2D have lower degree of EAT and better cardiac function,¹²⁴ indicating that the adipose load including EAT is a factor in mediating cardiac dysfunction and, in particular, mediating derangements in left ventricle (LV) mass and volume.⁷⁷ EAT has also been associated with diastolic dysfunction in patients with newly diagnosed T2D,¹²³ as well as with longer diabetes duration.³² A few studies also indicate a role for cardiac fat in cardiac systolic dysfunction, both in general,¹⁰⁸ and in patients with T2D specifically.³²

Taken together, there is considerable evidence to suggest that EAT is associated with an increased risk of CVD in general, and in patients with T2D in particular. EAT is also associated with reduced diastolic function in general and in T2D, and, although only few studies exist, there is emerging evidence of a role for EAT in systolic heart failure (Figure 1). Despite the clear evidence of EAT being a biomarker of heart disease and CVD, the question of whether T2D aggravates the pathogenic potential of EAT remains controversial.

**Clinical potential of EAT in cardiovascular risk prediction**

From both mechanistic and epidemiological studies, it is clear that EAT is associated with increased cardiovascular risk, and some studies suggest that it may also have potential to guide clinical decision making.³³,¹²⁷,¹³⁵ However, several aspects need clarification before the clinical relevance of EAT can be fully determined (Figure 2).

EAT can be measured by echocardiography, CT, or cardiac magnetic resonance imaging (MRI).¹³⁶ The measurement of EAT by echocardiography has several limitations, namely the discrimination of EAT and PAT can be difficult,³ EAT can be misinterpreted as pericardial effusion,² and the restricted acoustic window can impair a valid reflection of the total fat volume and fail to identify regional differences in fat distribution. Therefore, echocardiography exclusively allows for a rough two-dimensional estimation of the adipose tissue beds.¹,⁵ Conversely, CT and cardiac MRI are gold standards and allow for volumetric quantifications of EAT.¹³⁶ However, quantification in clinical practice, even by the gold standard, is challenging because of lack of sensitivity and specificity, and because it is technically difficult and there is a possibility for high noise and confounding due to, for example, interference of heart beats, water content, and fat droplets from parenchymal cells during image acquisition.¹³⁷,¹³⁸ Thus, a uniform standardized method for EAT quantification has not yet been determined, which has prevented the establishment of threshold values for physiological and pathological levels of EAT.

Another major challenge in the evaluation of EAT as a novel cardiac risk factor is the physiologic similarities between fat depots, which makes quantifying their independent contributions to cardiac risk difficult.⁷⁷,¹²⁵ Whereas some causal evidence of an independent role of EAT in the development of CVD has been obtained in animal studies,⁶² it is generally lacking in humans due to the difficulty in specifically targeting the EAT. Despite a previous study by our group that indicated cardiac fat was associated with CVD and all-cause mortality independently of BMI,³¹ it remains to be fully clarified whether EAT performs better than traditional anthropometric risk markers (e.g., BMI or waist circumference) or other visceral fat depots in predicting CVD risk.
For EAT to be a clinically important risk factor, we need to understand how the depot can be modified. Emerging evidence shows that EAT can be reduced by pharmacological therapies including GLP-1 analogues and SLGT2 inhibitors. It is, however, not known whether the cardioprotective effects of these drugs are mediated through the reductions in EAT. Whether EAT can also be targeted by lifestyle modifications for example, exercise, has been controversial, but recent studies support this idea. A recent study by our group suggests that exercise training reduces both EAT and PAT, without a change in total fat mass, indicating that exercise training may be a means to specifically target these fat depots. We also identified that the mechanism by which exercise targets EAT is through an IL-6 dependent mechanism, since blocking of the IL-6 receptor by Tocilizumab (a human monoclonal antibody) abolished exercise-induced EAT reductions. This disclosure of one of the mechanisms regulating EAT is important in order to find potential novel treatment targets. In general, both mechanistic and large longitudinal studies and properly designed intervention studies are needed to identify ways to specifically target EAT.

Overall, we now know from several observational studies that EAT shows promise as a modifiable cardiac risk factor. The underlying mechanisms by which EAT may accelerate atherosclerosis and myocardial damage have also been investigated in several studies and summarized in excellent recent reviews by Packer, Iacobellis and others, who shaped the idea that EAT plays a critical role as a metabolic transducer of systemic inflammation and thereby exerts deleterious effects on the myocardium and coronary arteries. Despite this, there are several aspects to be clarified before we understand whether EAT is a clinically relevant risk factor that will improve risk stratification and guide future clinical decision-making. Some essential aspects will be to establish how, and at what molecular phenotype of physiological vs. pathophysiological EAT and PAT
Since EAT and PAT biopsies are obtained from patients undergoing open heart surgery, they represent pathophysiological adipose tissue from patients. In order to understand the physiological functions of EAT and PAT, we need to investigate the depots in healthy individuals. This may be possible with the advances in cardiac imaging that allow for functional assessment of EAT and PAT (e.g. inflammation and browning).

Physiological properties of EAT vs. PAT and within-depot differences
EAT and PAT are often not or only inconsistently discriminated. Their individual importance in the development of CVD needs to be determined in translational in vitro, in vivo and human studies.

Clinical relevance of EAT and PAT
The clinical relevance of EAT and the contribution by PAT have not robustly been determined. Despite a few important papers, it is not firmly established whether EAT adds incremental predictive value to traditional CVD risk factors. EAT threshold values have not been identified consistently, and we do not know whether the physiological status of EAT (e.g. inflamed vs. non-inflamed EAT) or the total volume of EAT is the superior cardiac risk measure. Moreover, even though MRI/CT are golden standards and superior to echocardiography a standardized measurement method is lacking. Additionally, we do not know the importance of PAT in CVD risk prediction. As most work is done in patients with prevalent/suspected CVD, we do not know whether EAT and PAT play a role in cardiac risk prediction in populations at different risk stages (e.g. patients with vs. without T2D), and whether threshold values are similar in these populations.

Targeting EAT, PAT and VAT specifically
Given that visceral and cardiac adipose tissue is of particular importance for cardiac disease pathogenesis we need to investigate how these depots can be targeted specifically. Moreover, the various mechanisms regulating adipose tissue should be identified to find novel treatment targets.
location, this depot should be measured, whether we need to measure the total amount of fat (EAT + PAT) or rather the physiological state (e.g. inflammatory or brown fat activity), and whether EAT can be used in both males and females, and in the general population or only in sub-populations, for example, high-risk patients with T2D. We also need to understand how, and to what degree, EAT should be targeted to translate into clinically relevant reductions in cardiovascular risk (Figure 2).

**Conclusion**

EAT and PAT are emerging as potential clinically relevant cardiovascular risk markers, but several unanswered questions remain about these regional depots. The next leap forward will be to clearly establish the clinical relevance of EAT and PAT and their relative contributions to CVD and the predictive potential, both in the general population and in patients with T2D. Subsequently modifying EAT and PAT may become targets to reduce the excess cardiovascular morbidity and mortality in diabetes and obesity.

**Author Contribution(s)**

Regitse Højgaard Christensen: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing-original Draft; Writing-review & editing.

Bernt Johan von Scholten: Conceptualization; Supervision; Writing-review & editing.

Louise Lang Lehrskov: Conceptualization; Writing-review & editing.

Peter Rossing: Conceptualization; Writing-review & editing.

Peter Godsk Jørgensen: Conceptualization; Investigation; Supervision; Writing-review & editing.

**Conflict of interest statement**

The authors declare that there is no conflict of interest associated with this manuscript. PR has received consultancy and/or speaking fees (to his institution) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi Aventis, and Vifor.

**Funding**

Research grants from AbbVie, AstraZeneca and Novo Nordisk. BJvS is now employed at Novo Nordisk and has equity interest in Novo Nordisk. PGJ reports having received lecture fees from Novo Nordisk.

**ORCID iDs**

Regitse Højgaard Christensen https://orcid.org/0000-0001-5316-5341

Peter Godsk Jørgensen https://orcid.org/0000-0002-1217-8944

**References**

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019; 157: 107843.

2. Fox CS, Coady S, Sorlie PD, et al. Trends in cardiovascular complications of diabetes. *JAMA* 2004; 29: 2495–2499.

3. Barr ELM, Zimmet PZ, Welborn TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian diabetes, obesity, and lifestyle study (AusDiab). *Circulation* 2007; 116: 151–157.

4. Kannel WB and McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979; 241: 2035–2038.

5. Kannel WB and McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979; 2: 120–126.

6. Kannel WB, Hjortland M and Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; 34: 29–34.

7. Saeedi P, Salpea P, Karuranga S, et al. Mortality attributable to diabetes in 20–79 years old adults, 2019 estimates: results from the international diabetes federation diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. Epub ahead of print 15 February 2020. DOI: 10.1016/j.diabres.2020.108086.

8. Cavender MA, Steg PG, Smith SC Jr, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry. *Circulation* 2015; 132: 923–931.
9. Chen HF, Ho CA and Li CY. Risk of heart failure in a population with type 2 diabetes versus a population without diabetes with and without coronary heart disease. *Diabetes Obes Metab* 2019; 21: 112–119.

10. Franco OH, Steyerberg EW, Hu FB, *et al.* Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med* 2007; 167: 1145–1151.

11. Preis SR, Hwang SJ, Coady S, *et al.* Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham heart study, 1950 to 2005. *Circulation* 2009; 119: 1728–1735.

12. Boudina S and Abel ED. Diabetic cardiomyopathy, causes and effects. *Rev Endocr Metab Disord* 2010; 11: 31–39.

13. Bussey CT, de Leeuw AE and Lamberts RR. Increased haemodynamic adrenergic load with isoflurane anaesthesia in type 2 diabetic and obese rats in vivo. *Cardiovasc Diabetol* 2014; 13: 161.

14. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard lecture 2009. *Diabetologia* 2010; 53: 1270–1287.

15. Neeland IJ, Ross R, Després JP, *et al.* Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol* 2019; 7: 715–725.

16. Després JP and Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; 444: 881–887.

17. Després JP, Moorjani S, Lupien PJ, *et al.* Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Atherosclerosis* 1990; 10: 497–511.

18. Kim SH, Després JP and Koh KK. Obesity and cardiovascular disease: friend or foe? *Eur Heart J* 2016; 37: 3560–3568.

19. Wende AR and Abel ED. Lipotoxicity in the heart. *Biochim Biophys Acta* 2010; 1801: 311–319.

20. Tchkonia T, Thomou T, Zhu Y, *et al.* Mechanisms and metabolic implications of regional differences among fat depots. *Cell Metab* 2013; 17: 644–656.

21. Oikonomou EK and Antoniades C. The role of adipose tissue in cardiovascular health and disease. *Nat Rev Cardiol* 2019; 16:83–99.

22. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* 2010; 11: 11–18.

23. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr* 1956; 4: 20–34.

24. Arner P. Human fat cell lipolysis : biochemistry, regulation and clinical role. *Best Pract Res Clin Endocrinol Metab* 2005; 19: 471–482.

25. Li Y, Liu B, Li Y, *et al.* Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2019; 18: 3.

26. Packer M. Critical role of the epicardium in mediating cardiac inflammation and fibrosis in patients with type 2 diabetes. *Diabetes Obes Metab* 2019; 21: 1765–1768.

27. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol* 2018; 71: 2360–2372.

28. Mazurek T, Zhang L, Zalewski A, *et al.* Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460–2466.

29. Mazurek T and Opolski G. Pericoronary adipose tissue: a novel therapeutic target in obesity-related coronary atherosclerosis. *J Am Coll Nutr* 2015; 34: 244–254.

30. Noyes AM, Dua K, Devadoss R, *et al.* Cardiac adipose tissue and its relationship to diabetes mellitus and cardiovascular disease. *World J Diabetes* 2014; 5: 868–876.

31. Christensen RH, von Scholten BJ, Hansen CS, *et al.* Epicardial, pericardial and total cardiac fat and cardiovascular disease in type 2 diabetic patients with elevated urinary albumin excretion rate. *Eur J Prev Cardiol* 2017; 24: 1517–1524.

32. Christensen RH, Hansen CS, von Scholten BJ, *et al.* Epicardial and pericardial adipose tissues are associated with reduced diastolic and systolic function in type 2 diabetes. *Diabetes Obes Metab* 2019; 21: 2006–2011.

33. Christensen RH, Scholten BJ Von, Hansen CS, *et al.* Epicardial adipose tissue predicts incident cardiovascular disease and mortality in patients with type 2 diabetes. *Cardiovasc Diabetol* 2019; 18: 114.

34. Iacobellis G. Local and systemic effects of the pericardial adipose tissue: a novel therapeutic target in obesity-related coronary atherosclerosis. *Circulation* 2003; 108: 2460–2466.

35. Christensen RH, Scholten BJ, Hansen CS, *et al.* Epicardial adipose tissue predicts incident cardiovascular disease and mortality in patients with type 2 diabetes. *Cardiovasc Diabetol* 2019; 18: 114.
36. Antonopoulos AS and Antoniades C. The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles. *J Physiol* 2017; 595: 3907–3917.

37. Cherian S, Lopaschuk GD and Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. *Am J Physiol Endocrinol Metab* 2012; 303: e937–e949.

38. Schindler TH. Epicardial adipose tissue: a new cardiovascular risk marker? *Int J Cardiol* 2019; 278: 263–264.

39. Yudkin JS, Eringa E and Stehouwer CDA. “Vasocrine” signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 2005; 365: 1817–1820.

40. Iacobellis G, Malavazos AE and Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol* 2011; 43: 1651–1654.

41. Marchington JM, Mattacks CA and Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. *Comp Biochem Physiol B* 1989; 94: 225–232.

42. Smith HL and Willius FA. Adiposity of the heart: a clinical and pathologic study of one hundred and thirty-six obese patients. *Arch Intern Med* 1933; 52: 911–931.

43. Ng ACT, Strudwick M, van der Geest RJ, et al. Impact of epicardial adipose tissue, left ventricular myocardial fat content, and interstitial fibrosis on myocardial contractile function. *Circ Cardiovasc Imaging* 2018; 11: e007372.

44. Kankaanpää M, Lehto HR, Pärkkä JP, et al. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. *J Clin Endocrinol Metab* 2006; 91: 4689–4695.

45. Malavazos AE, Di Leo G, Secchi F, et al. Relation of echocardiographic epicardial fat thickness and myocardial fat. *Am J Cardiol* 2010; 105: 1831–1835.

46. Antonopoulos AS and Antoniades C. Cardiac magnetic resonance imaging of epicardial and intramyocardial adiposity as an early sign of myocardial disease. *Circ Cardiovasc Imaging* 2018; 11: e008083.

47. Blumensatt M, Fahlbusch P, Hilgers R, et al. Secretory products from epicardial adipose tissue from patients with type 2 diabetes impair mitochondrial β-oxidation in cardiomyocytes via activation of the cardiac renin–angiotensin system and induction of miR-208a. *Basic Res Cardiol* 2017; 112: 2.

48. Pezeshkian M and Mahatabpour MR. Epicardial and subcutaneous adipose tissue fatty acids profiles in diabetic and non-diabetic patients candidate for coronary artery bypass graft. *Bioimpacts* 2013; 3: 83–89.

49. Greulich S, Maxhera B, Vandenplas G, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation* 2012; 126: 2324–2334.

50. Les Laboratories Servier. Servier medical art [Internet], https://smart.servier.com/ (accessed 1 February 2020).

51. Iacobellis G, Pistilli D, Gucciardo M, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine* 2005; 29: 251–255.

52. Bambace C, Telema C, Zoico E, et al. Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men. *Cardiovasc Pathol* 2011; 20: e153–e156.

53. Chatterjee TK, Stoll LL, Denning GM, et al. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ Res* 2009; 104: 541–549.

54. Sacks HS, Fain JN, Cheema P, et al. Depot-specific overexpression of proinflammatory, redox, endothelial cell, and angiogenic genes in epicardial fat adjacent to severe stable coronary atherosclerosis. *Metab Syndr Relat Disord* 2011; 9: 433–439.

55. Imoto-Tsubakimoto H, Takahashi T, Ueyama T, et al. Serglycin is a novel adipocytokine highly expressed in epicardial adipose tissue. *Biochem Biophys Res Commun* 2013; 432: 105–110.

56. McAninch EA, Fonseca TL, Poggioli R, et al. Epicardial adipose tissue has a unique transcriptome modified in severe coronary artery disease. *Obesity (Silver Spring)* 2015; 23: 1267–1278.

57. Camarena V, Sant D, Mohseni M, et al. Novel atherogenic pathways from the differential transcriptome analysis of diabetic epicardial adipose tissue. *Nutr Metab Cardiovasc Dis* 2017; 27: 739–750.

58. Gaborit B, Ventecl Father, Ancel P, et al. Human epicardial adipose tissue has a specific transcriptomic signature depending on its
anatomical peri-atrial, peri-ventricular, or peri-coronary location. *Cardiovasc Res* 2015; 108: 62–73.

59. Salgado-Somoza A, Teijeira-Fernández E, Fernández AL, et al. Changes in lipid transport-involved proteins of epicardial adipose tissue associated with coronary artery disease. *Atherosclerosis* 2012; 224: 492–499.

60. Chechi K, Voisine P, Mathieu P, et al. Functional characterization of the Ucp1-associated oxidative phenotype of human epicardial adipose tissue. *Sci Rep* 2017; 7: 15566.

61. Chang HX, Zhao XJ, Zhu QL, et al. Removal of epicardial adipose tissue after myocardial infarction improves cardiac function. *Herz* 2018; 43: 258–264.

62. McKenney ML, Schultz KA, Boyd JH, et al. Epicardial adipose excision slows the progression of porcine coronary atherosclerosis. *J Cardiothorac Surg* 2014; 9: 2.

63. Wang CY, Li SJ, Wu TW, et al. The role of pericardial adipose tissue in the heart of obese minipigs. *Eur J Clin Invest* 2018; 48: e12942.

64. Sacks HS, Fain JN, Cheema P, et al. Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone. *Diabetes Care* 2011; 34: 730–733.

65. Bambace C, Sepe A, Zoico E, et al. Inflammatory profile in subcutaneous and epicardial adipose tissue in men with and without diabetes. *Heart Vessels* 2014; 29: 42–48.

66. Mráz M, Cinkajzlová A, Kloučková J, et al. Dendritic cells in subcutaneous and epicardial adipose tissue of subjects with type 2 diabetes, obesity, and coronary artery disease. *Mediators Inflamm* 2019; 2019: 5481725.

67. Santiago-Fernández C, Pérez-Belmonte LM, Millán-Gómez M, et al. Overexpression of scavenger receptor and infiltration of macrophage in epicardial adipose tissue of patients with ischemic heart disease and diabetes. *J Transl Med* 2019; 17: 95.

68. Sacks HS, Fain JN, Bahouth SW, et al. Adult epicardial fat exhibits beige features. *J Clin Endocrinol Metab* 2013; 98: E1448–E1455.

69. Sacks HS, Fain JN, Holman B, et al. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. *J Clin Endocrinol Metab* 2009; 94: 3611–3615.

70. Dozio E, Vianello E, Briganti S, et al. Increased reactive oxygen species production in epicardial adipose tissues from coronary artery disease patients is associated with brown-to-white adipocyte trans-differentiation. *Int J Cardiol* 2014; 174: 413–414.

71. Aldiss P, Davies G, Woods R, et al. ‘Browning’ the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol* 2017; 228: 265–274.

72. Moreno-Santos I, Pérez-Belmonte LM, Macías-González M, et al. Type 2 diabetes is associated with decreased PGC1α expression in epicardial adipose tissue of patients with coronary artery disease. *J Transl Med* 2016; 14: 243.

73. Iacobellis G. Epicardial and pericardial fat: close, but very different. *Obesity (Silver Spring)* 2009; 17: 625.

74. Chhabra L and Kowlgi NG. Cardiac adipose tissue: distinction between epicardial and pericardial fat remains important! *Int J Cardiol* 2015; 201: 274–275.

75. Sacks HS and Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007; 153: 907–917.

76. Guauque-Olarte S, Gaudreault N, Piché MÈ, et al. The transcriptome of human epicardial, mediastinal and subcutaneous adipose tissues in men with coronary artery disease. *PLoS One* 2011; 6: e19908.

77. Shah RV, Anderson A, Ding J, et al. Pericardial, but not hepatic, fat by computed tomography is associated with cardiovascular outcomes and structure: the Multi-Ethnic study of Atherosclerosis (MESA). *JACC Cardiovasc Imaging* 2017; 10: 1016–1027.

78. Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic study of Atherosclerosis (MESA). *Am J Clin Nutr* 2009; 90: 499–504.

79. Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham heart study. *Circulation* 2008; 117: 605–613.

80. Cheng VY, Dey D, Tamarappoo B, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* 2010; 3: 352–360.

81. Greif M, Leber AW, Saam T, et al. Determination of pericardial adipose tissue
increases the prognostic accuracy of coronary artery calcification for future cardiovascular events. *Cardiology* 2012; 121: 220–227.

82. Yang FS, Yun CH, Wu TH, et al. High pericardial and peri-aortic adipose tissue burden in pre-diabetic and diabetic subjects. *BMC Cardiovasc Disord* 2013; 13: 98.

83. Liberale L, Carbone F and Montecucco F. Pericardial adipose tissue and cardiovascular diseases: new insights from basic research. *Eur J Clin Invest* 2019; 49: e13052.

84. Sicari R, Sironi AM, Petz R, et al. Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study. *J Am Soc Echocardiogr* 2011; 24: 1156–1162.

85. Wang CP, Hsu HL, Hung WC, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. *Clin Endocrinol (Oxf)* 2009; 70: 876–882.

86. Tonbul HZ, Turkmen K, Kayikcioglu H, et al. Epicardial adipose tissue and coronary artery calcification in diabetic and non-diabetic end-stage renal disease patients. *Ren Fail* 2011; 33: 770–775.

87. Gaborit B, Kober F, Jacquier A, et al. Assessment of epicardial fat volume and myocardial triglyceride content in severely obese subjects: relationship to metabolic profile, cardiac function and visceral fat. *Int J Obes (Lond)* 2012; 36: 422–430.

88. Çetin M, Kocaman SA, Durakoçlugil ME, et al. Effect of epicardial adipose tissue on diastolic functions and left atrial dimension in untreated hypertensive patients with normal systolic function. *J Cardiol* 2013; 61: 359–364.

89. Rabkin SW. The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis. *Metab Syndr Relat Disord* 2014; 12: 31–42.

90. Iacobellis G, Diaz S, Mendez A, et al. Increased epicardial fat and plasma leptin in type 1 diabetes independently of obesity. *Nutr Metab Cardiovasc Dis* 2014; 24: 725–729.

91. Chambers MA, Shaibi GQ, Kapadia CR, et al. Epicardial adipose thickness in youth with type 1 diabetes. *Pediatr Diabetes* 2019; 20: 941–945.

92. Darabian S, Backlund JYC, Cleary PA, et al. Significance of epicardial and intrathoracic adipose tissue volume among type 1 diabetes patients in the DCCT/EDIC: a pilot study. *PLoS One* 2016; 11: e0159958.

93. Svanteson M, Holte KB, Haig Y, et al. Coronary plaque characteristics and epicardial fat tissue in long term survivors of type 1 diabetes identified by coronary computed tomography angiography. *Cardiovasc Diabetol* 2019; 18: 58.

94. Zobel EH, Winther SA, von Scholten BJ, et al. Myocardial flow reserve assessed by cardiac 82Rb positron emission tomography/computed tomography is associated with albumin excretion in patients with type 1 diabetes. *Eur Hear J Cardiovasc Imaging* 2019; 20: 796–803.

95. Kang J, Kim YC, Park JJ, et al. Increased epicardial adipose tissue thickness is a predictor of new-onset diabetes mellitus in patients with coronary artery disease treated with high-intensity statins. *Cardiovasc Diabetol* 2018; 17: 10.

96. Ojeda-Peña AC, Amador-Licona N, Rodriguez-Salazar E, et al. Comparison of epicardial fat thickness in diabetic patients compared to non-diabetics with acute myocardial infarction and ST-segment elevation (AMI-STEMI). *Gac Med Mex* 2016; 152: 345–349.

97. Vasques ACJ, Souza JRM, Pareja JC, et al. Epicardial and pericardial fat in type 2 diabetes: favourable effects of biliopancreatic diversion. *Obes Surg* 2015; 25: 477–485.

98. Peraza-Zaldivar JA, Suárez-Cuenca JA, Aceves-Millán R, et al. Pro-atherogenic mediators and subclinical atherogenesis are related to epicardial adipose tissue thickness in patients with cardiovascular risk. *J Int Med Res* 2017; 45: 1879–1891.

99. Seker T, Turkoglu C, HarbalIoglu H, et al. The impact of diabetes on the association between epicardial fat thickness and extent and complexity of coronary artery disease in patients with non-ST elevation myocardial infarction. *Kardiol Pol* 2017; 75: 1177–1184.

100. Chun H, Suh E, Byun AR, et al. Epicardial fat thickness is associated to type 2 diabetes mellitus in Korean men: a cross-sectional study. *Cardiovasc Diabetol* 2015; 14: 46.

101. Wang Z, Zhang Y, Liu W, et al. Evaluation of epicardial adipose tissue in patients of type 2 diabetes mellitus by echocardiography and its correlation with intimal medial thickness of carotid artery. *Exp Clin Endocrinol Diabetes* 2017; 125: 598–602.

102. Yazici D, Özben B, Yavuz D, et al. Epicardial adipose tissue thickness in type 1 diabetic patients. *Endocrine* 2011; 40: 250–255.
103. Versteelen MO, Takx RAP, Joosen IAPG, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. Eur Heart J Cardiovasc Imaging 2012; 13: 517–523.

104. Milanese G, Silva M, Bruno L, et al. Quantification of epicardial fat with cardiac CT angiography and association with cardiovascular risk factors in symptomatic patients: from the ALTER-BIO (alternative cardiovascular bio-imaging markers) registry. Diagnostic Interv Radiol 2019; 25: 35–41.

105. Zobel EH, Christensen RH, Winther SA, et al. Relation of cardiac adipose tissue to coronary calcification and myocardial microvascular function in type 1 and type 2 diabetes. Cardiovasc Diabetol 2020; 19: 16.

106. Akyürek Ö, Efe D and Kaya Z. Thoracic periaortic adipose tissue in relation to cardiovascular risk in type 2 diabetes mellitus. Wien Klin Wochenschr 2014; 126: 767–773.

107. Rado SD, Lorbeer R, Gatidis S, et al. MRI-based assessment and characterization of epicardial and paracardial fat depots in the context of impaired glucose metabolism and subclinical left-ventricular alterations. Br J Radiol 2019; 92: 20180562.

108. van Woerden G, Gorter TM, Westenbrink BD, et al. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail 2018; 20: 1559–1566.

109. Gullaksen S, Funck KL, Laugesen E, et al. Volumes of coronary plaque disease in relation to body mass index, waist circumference, truncal fat mass and epicardial adipose tissue in patients with type 2 diabetes mellitus and controls. Diab Vasc Dis Res 2019; 16: 328–336.

110. Al-Talabany S, Mordi I, Houston JG, et al. Epicardial adipose tissue is related to arterial stiffness and inflammation in patients with cardiovascular disease and type 2 diabetes. BMC Cardiovasc Disord 2018; 18: 31.

111. Mancio J, Oikonomou EK and Antoniades C. Perivascular adipose tissue and coronary atherosclerosis. Heart 2018; 104: 1654–1662.

112. Mahabadi AA, Massaro JM, Rosito GA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham heart study. Eur Heart J 2009; 30: 850–856.

113. Mahabadi AA, Lehmann N, Möhlenkamp S, et al. Noncoronary measures enhance the predictive value of cardiac CT above traditional risk factors and CAC score in the general population. JACC Cardiovasc Imaging 2016; 9: 1177–1185.

114. Mahabadi AA, Lehmann N, Kälsh H, et al. Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: the Heinz Nixdorf recall Study. Eur Heart J Cardiovasc Imaging 2014; 15: 863–869.

115. Mahabadi AA, Lehmann N, Kälsh H, et al. Association of epicardial adipose tissue with progression of coronary artery calcification is more pronounced in the early phase of atherosclerosis: results from the Heinz Nixdorf recall study. JACC Cardiovasc Imaging 2014; 7: 909–916.

116. Mahabadi AA, Berg MH, Lehmann N, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf recall study. J Am Coll Cardiol 2013; 61: 1388–1395.

117. Nerlekar N, Brown AJ, Muthalaly RG, et al. Association of epicardial adipose tissue and high-risk plaque characteristics: a systematic review and meta-analysis. J Am Heart Assoc 2017; 6: e006379.

118. Mancio J, Azevedo D, Saraiva F, et al. Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2018; 19: 490–497.

119. Reinhardt M, Cushman TR, Thearle MS, et al. Epicardial adipose tissue is a predictor of decreased kidney function and coronary artery calcification in youth- and early adult onset type 2 diabetes mellitus. J Endocrinol Invest 2019; 42: 979–986.

120. Kim HM, Kim KJ, Lee HJ, et al. Epicardial adipose tissue thickness is an indicator for coronary artery stenosis in asymptomatic type 2 diabetic patients: its assessment by cardiac magnetic resonance. Cardiovasc Diabetol 2012; 11: 83.

121. Chen WJY, Danad I, Rajimakers PG, et al. Effect of type 2 diabetes mellitus on epicardial adipose tissue volume and coronary vasomotor function. Am J Cardiol 2014; 113: 90–97.

122. Yerramasu A, Dey D, Venuraju S, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. Atherosclerosis 2012; 220: 223–230.
123. Kazlauskaite R, Doukky R, Evans A, et al. Predictors of diastolic dysfunction among minority patients with newly diagnosed type 2 diabetes. *Diabetes Res Clin Pract* 2010; 88: 189–195.

124. Levelt E, Pavlides M, Banerjee R, et al. Ectopic and visceral fat deposition in lean and obese patients with type 2 diabetes. *J Am Coll Cardiol* 2016; 68: 53–63.

125. Uygur B, Celik O, Ozturk D, et al. The relationship between location-specific epicardial adipose tissue volume and coronary atherosclerotic plaque burden in type 2 diabetic patients. *Kardiol Pol* 2017; 75: 204–212.

126. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 2018; 392: 929–939.

127. Topuz M and Dogan A. The effect of epicardial adipose tissue thickness on left ventricular diastolic functions in patients with normal coronary arteries. *Kardiol Pol* 2017; 75: 196–203.

128. Nakanshi K, Fukuda S, Tanaka A, et al. Persistent epicardial adipose tissue accumulation is associated with coronary plaque vulnerability and future acute coronary syndrome in non-obese subjects with coronary artery disease. *Atherosclerosis* 2014; 237: 353–360.

129. Doesch C, Haghi D, Flüchter S, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson* 2010; 12: 40.

130. Park HE, Choi SY and Kim M. Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography. *BMC Cardiovasc Disord* 2014; 14: 3.

131. Fontes-Carvalho R, Fontes-Oliveira M, Sampaio F, et al. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. *Am J Cardiol* 2014; 114: 1663–1669.

132. Watanabe K, Kishino T, Sano J, et al. Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction. *Heart Vessels* 2016; 31: 1010–1015.

133. Cheng VY. Plugging epicardial fat into a prediction algorithm. *Circ Cardiovasc Imaging* 2019; 12: e008629.

134. Liu CY, Redheuil A, Ouwerkerk R, et al. Myocardial fat quantification in humans: evaluation by two-point water-fat imaging and localized proton spectroscopy. *Magn Reson Med* 2010; 63: 892–901.

135. Iacobellis G. Epicardial fat: a new cardiovascular therapeutic target. *Curr Opin Pharmacol* 2016; 27: 13–18.

136. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol* 2018; 17: 6.

137. Iacovelli G. Epicardial fat: a new cardiovascular therapeutic target. *Curr Opin Pharmacol* 2016; 27: 13–18.

138. Liu CY, Redheuil A, Ouwerkerk R, et al. Myocardial fat quantification in humans: evaluation by two-point water-fat imaging and localized proton spectroscopy. *Magn Reson Med* 2010; 63: 892–901.

139. Iacobellis G. Epicardial fat: a new cardiovascular therapeutic target. *Curr Opin Pharmacol* 2016; 27: 13–18.
146. Gonzalez GF, Rodriguez MAR, Pareja MAR, et al. A home-based treadmill training reduced epicardial and abdominal fat in postmenopausal women with metabolic syndrome. *Nutr Hosp* 2014; 30: 609–613.

147. Christensen RH, Wedell-Neergaard AS, Lehrskov LL, et al. Effect of aerobic and resistance exercise on cardiac adipose tissues: secondary analyses from a randomized controlled trial. *JAMA Cardiol* 2019; 4: 778–787.

148. Christensen RH, Lehrskov LL, Wedell-Neergaard AS, et al. Aerobic exercise induces cardiac fat loss and alters cardiac muscle mass through an interleukin-6 receptor-dependent mechanism: cardiac analysis of a double-blind randomized controlled clinical trial in abdominally obese humans. *Circulation*. 2019; 140: 1684–1686.

149. Packer M. Disease-treatment interactions in the management of patients with obesity and diabetes who have atrial fibrillation: the potential mediating influence of epicardial adipose tissue. *Cardiovasc Diabetol* 2019; 18: 121.

150. Iacobellis G and Mahabadi AA. Is epicardial fat attenuation a novel marker of coronary inflammation? *Atherosclerosis* 2019; 284: 212–213.

151. Christensen RH, Lehrskov LL, Wedell-Neergaard AS, et al. Aerobic exercise induces cardiac fat loss and alters cardiac muscle mass through an interleukin-6 receptor-dependent mechanism: cardiac analysis of a double-blind randomized controlled clinical trial in abdominally obese humans. *Circulation*. 2019; 140: 1684–1686.

149. Packer M. Disease-treatment interactions in the management of patients with obesity and diabetes who have atrial fibrillation: the potential mediating influence of epicardial adipose tissue. *Cardiovasc Diabetol* 2019; 18: 121.