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Review

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

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***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

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## Introduction

Diabetes is one of the fastest-growing health challenges, with 463 million diagnosed today and rising to an estimated 700 million by 2045.[1] Type 2 diabetes (T2D) is by far the most prevalent subtype, accounting for 90% of all cases of diabetes.[1] Patients with T2D have 2- to 4-fold increased risk of cardiovascular disease (CVD) and heart failure,[2–6] and, in 2019, more than 4 million people died globally from diabetes-related complications,[7] namely CVD and heart failure.[8–11] 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.[12–19] Traditionally, obesity [defined as body mass index (BMI) $>$ 30 kg/m$^2$] *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, stromo-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 collegues in 2004.[28] They showed that, in patients with coronary artery disease (CAD), EAT has a higher

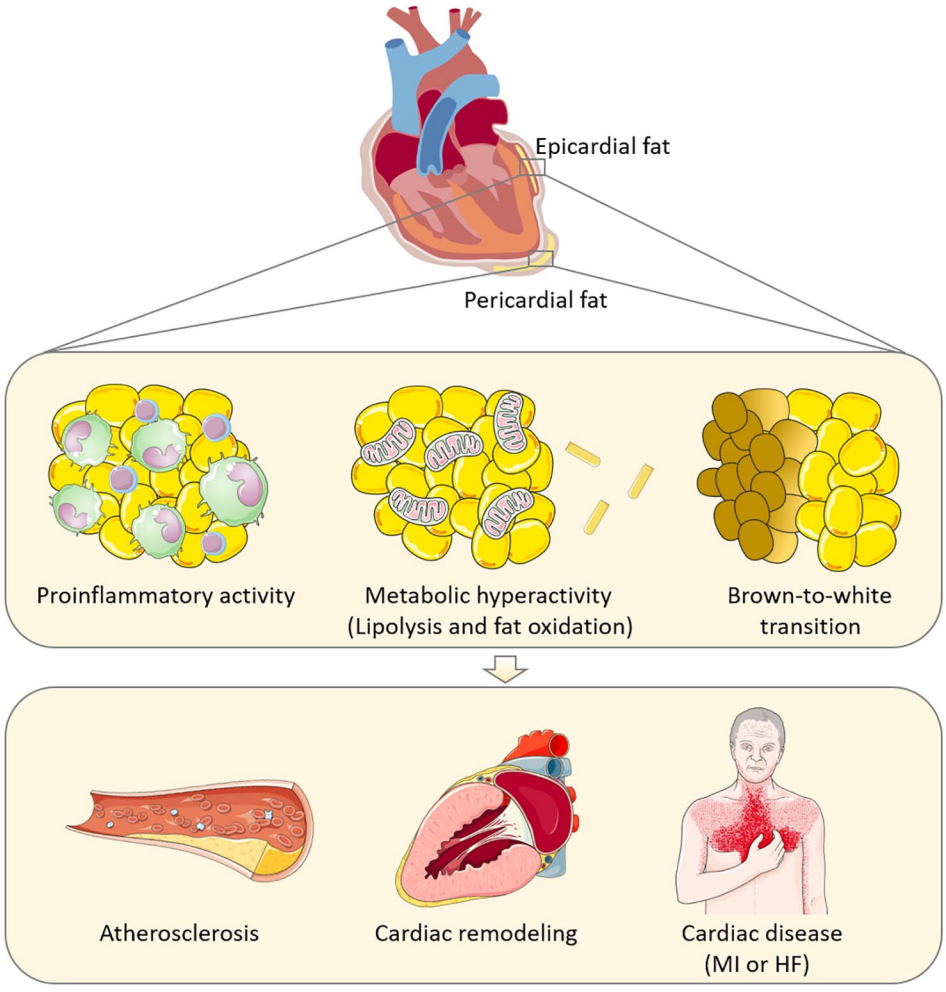


**Figure 1.** Mechanisms whereby epicardial (and potentially also pericardial) adipose tissue expansion in T2D may accelerate atherosclerosis, myocardial remodeling and diastolic dysfunction, MI, or HF. Clipart provided by Servier Medical Art.[50]
HF, heart failure; MI, myocardial infarction; T2D, type 2 diabetes.

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.[28] Moreover, adiponectin expression was found to be lower in EAT from patients with CAD compared with non-CAD patients,[51] and was lower in EAT compared with SAT.[52] Chatterjee *et al.* expanded the adipokine list by demonstrating that cultured EAT adipocytes secrete IL-8.[53] 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.[31] 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,[54–58] and indicated that EAT is more inflamed compared with intra-abdominal VAT.[55] 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.[59] Moreover, a few studies have shown that the secretome of EAT disrupts cardiomyocyte metabolism,[47] depresses cardiomyocyte contractile function,[49] and alters expression of adhesion markers of primary cardiac endothelial cells.[60] A recent intervention study in a rat model of myocardial infarction (MI) showed that surgical removal of EAT improves myocardial function following MI.[61]

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.[62] Obese mice fed a high fat diet specifically induced a pro-inflammatory adipokine state and increased adipocyte size in pericardial fat.[63] 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,[64] 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.[65] 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,[66] whereas infiltrating pro-inflammatory macrophages were upregulated in EAT from patients with T2D. [67] 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.[60,68,69] 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.[70] 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,[71] 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[72] (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).[30,73–75] PAT is supplied by blood from the thoracic vasculature and it is not in direct contact with the myocardium.[30,73,74] 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.[21,36] Despite these marked differences of the depots, EAT and PAT have similar transcriptional profiles,[76] 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.[31,77–82] Similar to EAT, PAT has a higher expression of pro-inflammatory adipokines compared with intraabdominal VAT.[63,83] While one paper suggests PAT to be more closely associated with cardiovascular risk factors compared with EAT,[84] others have found that PAT alone does not predict future CVD and all-cause mortality in patients with diabetes.[31] 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 $cm^3$ in patients with T2D compared with 123.4 ± 41.8 $cm^3$ in patients without diabetes.[85] This finding of high amounts of EAT in patients with T2D was confirmed by several subsequent studies,[86–88] including a recent large cohort of 1000 patients.[32] In 2014, a meta-analysis confirmed the association of EAT and parameters of the metabolic syndrome,[89] 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 |
|---|---|---|---|---|---|---|
| | | T2D | Controls | | | |
| 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 | 4.42 ± 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 mm¤ | 5.7 mm¤ | 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-Zaldivar *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) $cm^3$ | 116.0 (91.6–139.4) $cm^3$ | 60 (17 *versus* 43) | CT | 2011 |
| Versteylen *et al.*[103] | T2 | 98 ± 41 $cm^3$ | 75 ± 34 $cm^3$ | 292 (83 *versus* 209) | CT | 2012 |
| Wang *et al.*[85] | T2 | 166.1 ± 60.6 $cm^3$ | 123.4 ± 41.8 $cm^3$ | 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.*[93] | T1 | 52.3 (36.1–65.5) $cm^3$ | 55 (38.3–79.6) $cm^{3a}$ | 148 (88 *versus* 60) | CT | 2019 |
| Zobel *et al.*[105] | T1 | 106 ± 78 ml | 99 ± 61 $ml^{a,b}$ | 90 (60 *versus* 30) | CT | 2020 |
| Zobel *et al.*[105] | T2 | 228 ± 97 ml | 99 ± 61 $ml^{b}$ | 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 $cm^3$ | 68.9 ± 37.7 $cm^3$ | 152 (90 *versus* 62) | CT | 2015 |
| Gaborit *et al.*[87] | T2 | 213 ± 34 ml | 141 ± 18 ml | 30 (13 *versus* 17) | MR | 2012 |
| Rado *et al.*[107] | T2 | 7.7 (5, 10) $cm^{3\#}$ | 10.3 (7, 14) $cm^{3\#x}$ | 272 (52 *versus* 220) | MR | 2019 |
| van Woerden *et al.*[108] | T2 | 116 ± 10 ml/m# | 100 ± 10 ml/m# | 64 (28 *versus* 36) | MR | 2018 |
| Gullaksen *et al.*[109] | T2 | 119 ± 49 $mm^3$ | 86 ± 40 $mm^3$ | 103 (44 *versus* 59) | CT | 2019 |

IQR [range].
¤No SD or IQR available.
#Estimated or partly estimated from a figure.
[a]Not significant.
[b]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 I diabetes.

**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.
[a]Not significant.
[b]Total cardiac fat (EAT+PAT).

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 findings,[31,119] 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.

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.

| |
|---|
| **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[18,107] and browning[18,149]). |
| **Physiological properties of EAT vs. PAT and within-depot differences** |
| EAT and PAT are often not or only inconsistently discriminated.[33] 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,[18,150] 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[18]) or the total volume of EAT[150] or EAT at a specific location[92,106] 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. |

**Figure 2.** Future questions for epicardial and pericardial adipose tissue research.
CT, computed tomography; CVD, cardiovascular disease; EAT, epicardial adipose tissue; MRI, magnetic resonance imaging; PAT, pericardial adipose tissue.

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.[139–143] 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,[144] but recent studies support this idea.[145,146] 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.[147] 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.[148] 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,[26,27,149] Iacobellis[34,150] and others,[21,29,128,151] who shaped the idea that EAT plays a critical role as a metabolic transducer of systematic 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

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.

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## 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.

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