

Cardiac adipose tissue and its relationship to diabetes mellitus and cardiovascular disease

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Abstract

Type-2 diabetes mellitus (T2DM) plays a central role in the development of cardiovascular disease (CVD). However, its relationship to epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT) in particular is important in the pathophysiology of coronary artery disease. Owing to its close proximity to the heart and coronary vasculature, EAT exerts a direct metabolic impact by secreting proinflammatory adipokines and free fatty acids, which promote CVD locally. In this review, we have discussed the relationship between T2DM and cardiac fat deposits, particularly EAT and PAT, which together exert a big impact on the cardiovascular health.

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Key words: Epicardial adipose tissue; Pericardial adipose tissue; Type 2 diabetes; Cardiovascular disease

Core tip: Diabetes, a cardiovascular disease equivalent, has considerable effects on the cardiovascular system. Its impact works systemically, but may have more association with epicardial and pericardial adipose tissue

locally at the level of the heart. These cardiac tissues have great interplay with diabetic patients and have potential to influence cardiovascular disease.

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INTRODUCTION

More than 25 million United States adults have type-2 diabetes mellitus (T2DM) and this figure will likely reach 50 million by 2050^[1,2]. The relationship between metabolic diseases such as T2DM and regional fat deposits, particularly epicardial adipose tissue (EAT) and pericardial adipose tissue (PAT), play an important role in the development of cardiovascular diseases (CVD). Both EAT and PAT are a subset of visceral adipose tissue (VAT) associated with T2DM. They are metabolically active visceral fat deposits found around the heart^[3], that are strongly associated with CVD including coronary artery disease (CAD) and the development of cardiac arrhythmias, predominantly due to the secretion of pro-inflammatory mediators and cytokines^[4]. In this paper, we review the emerging evidence of impact of T2DM on VAT and the specific role of EAT and PAT both as a cardiac risk marker and as a potentially active player in the development of cardiovascular pathology.

RESEARCH

We searched MEDLINE and PubMed for original articles published between 1984 and 2014, focusing on epicardial adipose tissue and type 2 diabetes mellitus. The search terms we used, alone or in combination, were

“epicardial fat”, “epicardial adipose tissue”, “pericardial fat”, “pericardial adipose tissue”, “insulin resistance”, “type 2 diabetes mellitus”, “metabolic syndrome”, “cardiovascular disease”, “coronary artery disease”, “congestive heart failure”, and “atrial fibrillation”, which yielded 121 articles. All articles identified were English-language, full-text papers and abstracts. We finally selected 87 articles, which were relevant to our current discussion.

T2DM AND CARDIAC VISCERAL FAT

Cardiac disease is the leading cause of death in T2DM, and many have sought to determine the mechanism of development of cardiac dysfunction^[5]. Interestingly, diabetic patients with no evidence of CAD or hypertension have also been found with cardiac abnormalities, even when they are asymptomatic. Studies have shown that the metabolic derangements in T2DM primarily contribute to the cardiac problems^[6], which, in part, are due to increase in visceral fat deposits and being frequently accompanied by disorders of glucose metabolism^[7]. Obesity, specifically abdominal VAT, is an independent risk factor for CVD^[8], and is prominent in patients with T2DM^[7]. Moreover, studies have shown the correlation between excessive adipose tissue deposition and development of diabetes^[9]. Central and VAT is associated with endocrine disorders due to the release of substances such as free fatty acids (FFA), leptin, adiponectin, pro-inflammatory agents, and decreased anti-inflammatory factors. As a result, it often results in unfavorable glucose metabolism and T2DM^[10,11]. It has also been well demonstrated that pre-diabetic and diabetic patients are associated with significantly higher PAT burden compared to normoglycemic patients^[12]. In a cross sectional study, the impact of obesity and T2DM on adipocytokines (adiponectin, leptin and resistin), inflammatory markers [tumor necrosis factor- α (TNF- α), Interleukin (IL)-6 and high sensitive C-reactive protein (HsCRP)] were evaluated^[13]. Obesity was found to significantly lower adiponectin levels, while increasing leptin and IL-6 levels along with HsCRP. There is also a strong association between the increased expression of resistin, another adipocyte-secreted factor, and insulin resistance^[14], with the burden of EAT volume being greater in individuals with metabolic syndrome, increased insulin resistance and diabetes mellitus^[15,16], and is significantly higher in patients with T2DM than in non-diabetic subjects^[14]. The serum profile of coronary artery bypass grafting patients showed significantly higher levels of HsCRP and lower levels of adiponectin compared to body mass index (BMI)-matched controls, supporting the role of VAT in causation of systemic inflammation^[17]. Adiponectin has been shown to have a protective role with anti-inflammatory properties suppressing TNF- α and IL-6^[13,18]. Hypoadiponectin levels in obesity along with elevated TNF- α , HsCRP and IL-6 were shown to correlate with insulin resistance seen in this population^[13]. Interestingly leptin and resistin levels were not shown to consistently correlate with insulin resistance.

EAT and omental fat were shown to have broadly comparable pathogenic mRNA profile^[17]. EAT and PAT are both forms of VAT, which store lipids and have demonstrated increased expression of the above mentioned hormones, chemokines and cytokines, with the addition of monocyte chemoattractant protein-1 and IL-1 β ^[19]. These adipokines also impair insulin-signaling pathways leading to insulin resistance and reduced nitric oxide (NO) synthesis, causing unopposed vasoconstriction^[20]. Thus, the endocrine function of EAT and PAT play a significant role in patients with metabolic syndrome. In fact, the examination of EAT and PAT found that PAT is associated with VAT and metabolic syndrome features such as T2DM, than that of EAT^[21]. On the other hand, EAT thickness showed independent positive correlation with metabolic parameters including postprandial glucose ($P = 0.049$), HbA1c level ($P < 0.001$), and homeostasis model assess of insulin resistance ($P = 0.047$)^[22]. EAT accumulation was seen to strongly correlate with serum fibroblast growth factor 21, which is known to improve insulin sensitivity despite an increment in its serum levels in T2DM patients. Thus, excessive EAT in T2DM patients may exert bivalent, unfavorable and adaptive effects on progression of cardiovascular diseases^[23].

In obese patients with T2DM, adipocytes from epicardial fat infiltrate the myocardium, which refers to a strong association of intra-myocardial fat content to the echocardiographic epicardial fat thickness. Similarly, EAT has been found to be significantly related to intra-abdominal visceral fat, suggested by echocardiographic studies^[24,25], and PAT may increase up to 400 g in T2DM patients (with 100 g in healthy lean people)^[26]. Yang *et al*^[12] demonstrated the burden of PAT in diabetic and pre-diabetic subjects, revealing that PAT volume was much higher in pre-diabetics and diabetics as compared to normoglycemic subjects.

However, it is important to distinguish EAT and PAT from obesity-specific lipotoxic cardiomyopathy, in which excessive fat proliferates inside cardiac muscle causing left ventricular remodeling and eventually cardiomyopathy. This develops after subcutaneous adipose tissues and VAT are unable to accommodate the excess fat in the obese patients leading to intracellular accumulation of lipids and FFA, eventually forming myocardial steatosis^[27].

ANATOMICAL, METABOLIC AND FUNCTIONAL DIFFERENCES BETWEEN EAT AND PAT

Epicardial and pericardial adipose tissue are close, however anatomically clearly different. EAT is not symmetrically distributed around the heart (Figure 1). EAT volume and thickness varies depending on the location (Figure 2). PAT (Figure 3) has a different embryonic origin than that of EAT as it originates from the embryonic primitive thoracic mesenchyme^[24], and clinically are different. In

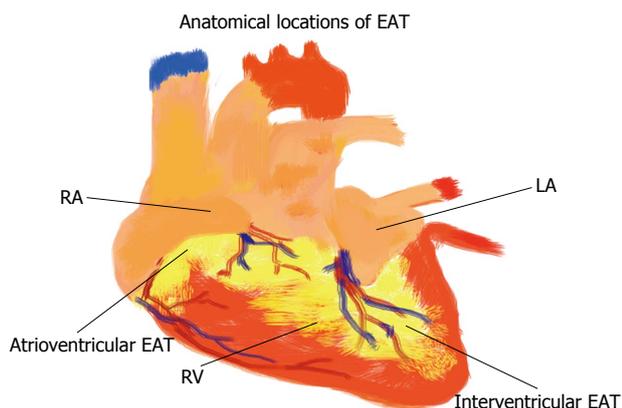


Figure 1 Anatomical locations of epicardial adipose tissue. RV: Right ventricle; RA: Right atrium; LA: Left atrium; EAT: Epicardial adipose tissue (yellow color refers to EAT).

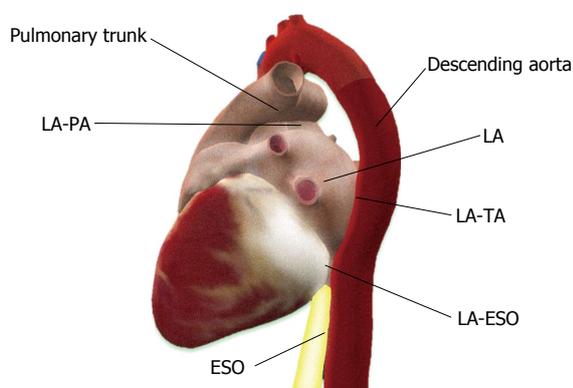


Figure 2 Periatrial epicardial adipose tissue around left atrium (heart in lateral axis view). LA-PA: Epicardial adipose tissue (EAT) between left atrium and pulmonary artery; LA-TA: EAT between left atrium and thoracic aorta; LA-ESO: EAT between left atrium and esophagus.

the existing literature, the terminologies have often been erroneously overlapped without clear differentiation between these two entities. Some suggest the use of a terminology, which encompasses three types of fat around the heart: epicardial, pericardial and paracardial fats. In this terminology, paracardial fat often refers to the fat located on the external surface of the parietal pericardium, while the term pericardial fat is used to represent EAT plus paracardial fat. It is important to be familiar with these terms to avoid confusion. In our opinion, it is rather more important to differentiate the “true pericardial fat” from “paracardial fat” as these two have different endocrine and metabolic properties. The true pericardial fat (epi-pericardial fat) should encompass the epicardial and pericardial fat (*i.e.*, fat located above the myocardium and up to the parietal pericardium; epicardial fat being located between the outer wall of the myocardium and the visceral layer of pericardium and pericardial fat being located between the visceral and the parietal pericardium), while paracardial fat should clearly be considered as the fat located outside the parietal pericardium.

EAT is a metabolically active visceral fat deposit found around the heart, between the pericardium and

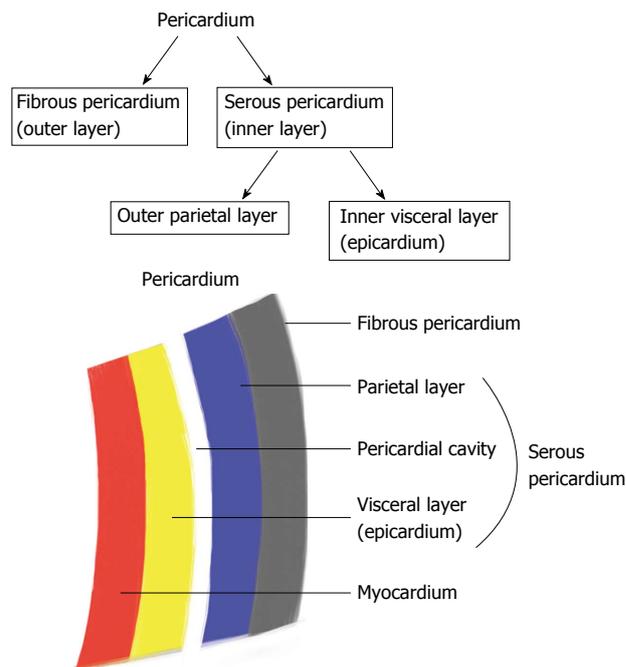


Figure 3 Pericardium/Pericardial layers.

myocardium^[3]. EAT can be found in highest concentration in the atrioventricular and interventricular grooves and alongside the coronary arteries, and lesser so around the atria, over the free wall of the right ventricle and over the apex of the left ventricle. PAT may be defined as EAT plus paracardial fat, whereas paracardial fat is located on the external surface of the parietal pericardium within the mediastinum^[28]. EAT varies from PAT and other local fat depots in the size of its adipocytes, where as epicardial adipocytes are smaller in size and high in number (high number of pre-adipocytes). The best imaging tool for quantification of both EAT and PAT remains uncertain. Their thicknesses and volumes can be evaluated by echocardiography, computed tomography (CT) or magnetic resonance imaging (MRI)^[24,29]. Due to distinct attenuation values of fat on chest or cardiac CT and MRI, EAT and PAT are both readily identified with ability to calculate the tissue volume and thickness. Furthermore, MRI accurately correlates with EAT and PAT seen on echocardiography imaging^[30].

Biochemically, EAT and PAT are different. Investigation into EAT and PAT suggests that these two tissues have different metabolic and physiologic properties^[31]. Under physiological situations, EAT is cardioprotective which can be explained by its anti-atherogenic/anti-inflammatory properties, high FFA release and uptake and low glucose requirements, serving as a major source of energy to the heart and thermoregulatory properties^[32]. It is also known to provide mechanical support to the coronary arteries as well as anti-toxic effects by protecting heart from high levels of FFA. In diabetics, lack of insulin impairs cardiac glucose transport and oxidation, resulting in FFA becoming the preferred means of energy supply^[33]. To make available this increased requirement

Table 1 Studies showing the relationship between pericardial adipose tissue and epicardial adipose tissue and the development of coronary artery disease

Ref.	Year	Diagnostic modality	Results
Taguchi <i>et al</i> ^[86]	2001	Computerized tomogram	Pericardial fat was the strongest independent variable for severity of CAD, determined by coronary angiogram
Jeong <i>et al</i> ^[44]	2007	Echocardiogram	Epicardial fat thickness significantly correlated with the severity of CAD in patients with known CAD
Ahn <i>et al</i> ^[38]	2008	Echocardiogram	Epicardial adipose tissue was an independent predictor of CAD
Greif <i>et al</i> ^[36]	2009	Computerized tomogram	Patient with any coronary plaque showed a significantly higher pericardial adipose tissue volume compared to patients without coronary plaques
Shemirani <i>et al</i> ^[40]	2012	Echocardiogram	Confirms the presence of association between epicardial fat thickness and severity of CAD

CAD: Coronary artery disease.

of the heart for FFA, the diabetic heart upregulates its luminal lipoprotein lipase (LPL) activity, which can result in abnormal FFA supply and utilization by the heart tissue, potentially initiating cardiac dysfunction^[33]. Importantly, EAT has low levels of LPL and acetyl-CoA as compared to subcutaneous fat^[34], though the cardio-protective role of PAT is not clear^[31]. Despite these protective qualities, EAT in excess can become cardio-toxic resulting in local inflammatory changes and cardiac dysfunction^[32,35]. In non-diabetic patients with excessive EAT, the presence of fatty acid binding protein-4 in epicardial adipocytes, and its increased expression, promotes the development of metabolic syndrome^[32] and T2DM.

CARDIAC ADIPOSITY, DIABETES MELLITUS AND CAD

PAT and EAT have firmly been recognized as a contributor to the development of CAD^[36-41], and several cross sectional studies (Table 1) have shown similar results. PAT is emerging as a novel risk factor for CVD development^[42] and progression^[43], as CAD has been shown to correlate with PAT more consistently than other general measures of adiposity like body mass index or waist circumference^[42]. PAT volume has been a predictor of increased death and disability for CVD^[44], and independently linked with coronary artery calcification (CAC)^[45]. EAT has also been shown to correlate with CAC^[43] and has a statistically significant correlation between EAT and CAC in both diabetic and non-diabetic patients ($P = 0.01$, $r = 0.60$; $P = 0.02$, $r = 0.38$, respectively)^[46]. The Multi-Ethnic Study of Atherosclerosis study showed a stronger correlation between PAT and the incidence of future coronary heart events in a group of patients without history of CAD, than that of other cardiac risk factors such as BMI or waist circumference^[42].

EAT has been studied more extensively than PAT. EAT differs from PAT, not only in its location, but also by its blood supply. EAT derives its blood supply from coronary circulation, whereas PAT is supplied by non-coronary sources^[32]. There is a functional and anatomic relationship between EAT and muscular components of the heart as these components share the same coronary blood supply, due to the lack of fascia separating the adi-

pose tissue and myocardial layers^[3]. Because of the highly metabolic paracrine and endocrine functions of EAT, it has been proposed to play a role in the pathogenesis of CVD by contributing to increased carotid intima media thickness (CIMT) in those with metabolic syndrome^[47], CAD^[37-41], increased left ventricle (LV) mass^[48] and diastolic dysfunction^[49,50]. The release of pro-inflammatory and pro-atherogenic factors into the circulation advancing CVD is more significantly linked to VAT accumulation, metabolic syndrome and other situations related to oxidative stress^[32]. Pathophysiological effects of abnormal EAT may be explained by the expression of an enzyme-sPLA2-IIA which is generally found in human atherosclerotic lesions^[32]. In patients with CAD, catalase levels in EAT are lower than in subcutaneous fat resulting in higher oxidative stress, which further contributes to atherosclerosis.

It is the close anatomical relationship between EAT and the coronary arteries, combined with its biologically active properties that participates in the pathogenesis of diabetic coronary atherosclerosis^[4,51]. Iacobellis *et al*^[52] demonstrated that the expression of anti-inflammatory and antiatherogenic properties of adiponectin was approximately 40% lower in the EAT of patients with CAD than in that of normal controls.

Apart from above, EAT was also shown to play an important role in the prediction of no-reflow phenomenon in ST elevation myocardial infarction treated with primary percutaneous intervention (PCI)^[53]. The no-reflow was defined as < 70% ST-segment resolution following primary PCI. EAT has also been shown to be one of the independent factors associated with restenosis post-stenting warranting target vessel revascularization^[54]. Smooth muscle proliferation, secondary to the local inflammatory mediators, have been postulated as mechanism of restenosis in this population^[54].

EAT volume also has a significant role in promoting CVD and was shown to be positively and independently related to coronary atherosclerotic burden^[55], and was significantly increased in patients with acute coronary syndrome^[14]. Multivariate logistic regression analysis indicated that EAT thickness was an independent indicator for significant coronary artery stenosis after adjusting for traditional risk factors (OR = 1.403, $P = 0.026$)^[22]

assessed by cardiovascular magnetic resonance imaging in asymptomatic T2DM patients. Echocardiographic measurement of EAT thickness ≥ 7 mm was shown to identify individuals with higher probability of coronary atherosclerosis^[56]. Furthermore, EAT thickness ≥ 5 mm in general population may identify individuals with higher likelihood of detectable carotid atherosclerosis, but did not have any significant association with CIMT^[57]. However, EAT thickness in patients with metabolic syndrome showed a linear positive correlation with CIMT^[47]. Similar association was also found in human immunodeficiency virus receiving highly active antiretroviral therapy^[58]. These studies establish that the correlation between EAT and CIMT is stronger in high-risk individuals prone to atherosclerosis than in the general population. It also demonstrates the existence of independent paracrine effects in addition to the endocrine effect, to account for the consistent association of EAT and coronary atherosclerosis^[59].

CARDIAC ADIPOSITY AND VENTRICULAR FUNCTION

EAT and associated inflammatory cytokines, particularly hypoadiponectin levels and reduced NO synthesis, may have direct effect on myocardium causing dysfunction independent of ischemic pathophysiology^[60]. PAT was shown to be significantly associated with LV diastolic dysfunction in people with CAD and normal ejection fraction independent of other risk factors including diabetes and hypertension^[61]. Variation in regional fat distribution has been reported in patients on peritoneal dialysis^[62]. Increased EAT thickness determined by echocardiogram in such patients was shown to be the most powerful determinant of LV diastolic dysfunction among other variables^[63]. In addition to the paracrine metabolic effect as discussed earlier, mechanical effect of increased PAT has also been shown to contribute to the pathophysiology of diastolic dysfunction^[63]. Additionally, patients with LV diastolic dysfunction had significantly increased EAT volumes^[64].

On contrary, in patients with congestive heart failure (CHF) and severely reduced left ventricular ejection fraction (LVEF), EAT has been found to be significantly reduced^[65]. LV function in such patients correlated best with EAT/Left Ventricular Remodeling Index ratio^[65], raising a possible protective role of EAT to remodeling myocardium. Khawaja *et al.*^[66] demonstrated similar results with a stepwise decrease in EAT volume from controls to patients with moderate CHF (LVEF 35%-55%) and severe heart failure (LVEF < 35%). Though the paracrine metabolic effects and possible role as source of FFA to myocardium in demand has been postulated as mechanism for this correlation^[65], the exact pathophysiology remains elusive. Further study is needed to access the possible confounding role of lipid lowering therapies to this finding in such patients.

CARDIAC ADIPOSITY, DIABETES MELLITUS AND ARRHYTHMOGENICITY

Obesity is a well-established risk factor for atrial fibrillation (AF), as altered atrial electrical function is considered an important mechanism for the relation of obesity and increased AF risk. Atrial tissue in diabetic subjects demonstrates persistent oxidative stress compared with nondiabetics; which can potentially play a role in the development of interatrial conduction delay^[67]. Evidence on the impact of EAT thickness, particularly in the area of posterior left atrium, is associated with persistent AF^[68,69]. PAT is also associated with a higher incidence of AF, both paroxysmal (OR = 1.11, 95%CI: 1.01-1.23, $P = 0.04$) and persistent (OR = 1.18, 95%CI: 1.05-1.33, $P = 0.004$), independent of other risk factors^[69]. PAT's unique anatomic proximity to the myocardium and atrial conduction system may modify atrial electrophysiology and promote subsequent risk for arrhythmogenesis^[70]. Based on PAT's influence on altered P-wave indices (PWI), potential mechanisms by which increases in PAT may lead to changes in atrial conduction include prolonged atrial depolarization, diminished voltage, and heterogeneous atrial activation related to fibrosis, hypertrophy, and fatty myocardial infiltration^[70].

Two independent studies reported significant association of pericardial fat volume with AF both paroxysmal and persistent even after adjustment for traditional risk factors^[69,71]. The possible mechanisms speculated were secondary to increase in left atrial size associated with pericardial fat^[72,73] and local inflammatory effects induced by pericardial adipose tissue as discussed earlier *via* paracrine and endocrine route. This speculation was based on the evidence that systemic inflammation marked by CRP was associated with presence of AF and also predicted the patients at risk for future development of AF^[74].

PWI and PAT were found to be associated independent of ectopic visceral and intra-thoracic fat depots^[70], supporting the role of PAT in atrial conduction. Voltage-dependent PWI (P-Wave amplitude, P wave area and P wave terminal force) may be enhanced by hypertrophy of left atrium seen with pericardial fat. At the same time it may also be decreased due to fibrosis and effects on summation vector secondary to insulation effect^[70]. The insulation effect does not affect the voltage-independent PWI (P wave duration and PR interval), however hypertrophy and fibrosis may still affect the conduction time^[70]. P-wave terminal force is more closely associated with pericardial fat than other voltage-dependent PWI^[70]. This is due to the fact that blocked posterior inter-atrial bundles seen with PAT causes anterior to posterior activation of left atrium resulting in a terminal negative deflection on the electrocardiogram in lead V1. PAT has been questioned to contribute to the P wave dispersion seen in obese individuals^[71].

With further advancements in imaging, thickness of the posterior peri-atrial fat pad between left atrium

and the esophagus was found to correlate with the AF burden^[68]. Their proximity to the pulmonary vein ostia would explain the correlation, as triggers for AF initiation are located in the pulmonary vein ostia^[75]. EAT total and inter-atrial septal thickness was shown to be related to left atrial volume independently even after adjustment for other confounding factors^[76]. PAT has also been associated with increased risk of AF recurrence after ablation^[77]. PAT volume has also been identified as a novel risk factor for post-operative AF after coronary artery bypass grafting^[78].

MANAGEMENT OF EAT AND PAT

As excessive cardiac adipose tissue have correlations with poor cardiovascular outcomes, research into possible reversal of the tissue has been studied. Weight loss through bariatric surgery and calorie restriction has shown a corresponding decrease in EAT volume and thickness. EAT thickness decreased in obese subjects who underwent an aggressive 6-mo long weight loss program (mean 20 kg) by adhering to a very low-calorie diet (900 kcal/d)^[79]. Similarly, weight loss after bariatric surgery (average weight loss of 40 kg) was associated with a decrease in EAT thickness^[80]. Conversely, the compared effects of pioglitazone and metformin treatment in T2DM patients demonstrated an increase in PAT volume in pioglitazone-treated patients after 24 wk^[81]. Nonetheless, the correlation between increased cardiac adipose tissue has been associated with several features of metabolic syndrome, including fasting insulin^[82]. Further studies are needed to show the effects of controlling these measures with changes in size of the cardiac adipose tissues.

CONCLUSION

Cardiac adipose tissue is metabolically active and associated with various metabolic derangements in the body leading to insulin resistance, atherosclerosis, metabolic syndrome and CVD. It has become clear that the adipose tissue around the heart is a critical indicator of CVD burden. Lifestyle and medical improvements may reduce this impact, as the evidence through the use of ultrasound has documented that weight loss is associated with a decrease in pericardial fat stores in both non-diabetic^[79,83,84] and diabetic^[85] subjects. In diabetics, metabolic derangements are significantly linked with cardiac adiposity, thus it should be considered screening for EAT or PAT as CVD risk factors in diabetic patients. Many aspects between EAT and PAT overlap. Clinicians and researchers must have a clear understanding of their physiological and pathological differences to expand on screening, managing and reducing the impact that EAT and PAT have on CVD.

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