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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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REVIEW

Targeting epicardial adipose tissue: A potential therapeutic strategy for heart failure with preserved ejection fraction with type 2 diabetes mellitus

Yu-Jiao Shi, Guo-Ju Dong, Ming Guo

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome with various comorbidities, multiple cardiac and extracardiac pathophysiologic abnormalities, and diverse phenotypic presentations. Since HFpEF is a heterogeneous disease with different phenotypes, individualized treatment is required. HFpEF with type 2 diabetes mellitus (T2DM) represents a specific phenotype of HFpEF, with about 45%-50% of HFpEF patients suffering from T2DM. Systemic inflammation associated with dysregulated glucose metabolism is a critical pathological mechanism of HFpEF with T2DM, which is intimately related to the expansion and dysfunction (inflammation and hypermetabolic activity) of epicardial adipose tissue (EAT). EAT is well established as a very active endocrine organ that can regulate the pathophysiological processes of HFpEF with T2DM through the paracrine and endocrine mechanisms. Therefore, suppressing abnormal EAT expansion may be a promising therapeutic strategy for HFpEF with T2DM. Although there is no treatment specifically for EAT, lifestyle management, bariatric surgery, and some pharmaceutical interventions (anti-cytokine drugs, statins, proprotein convertase subtilisin/kexin type 9 inhibitors, metformin, glucagon-like peptide-1 receptor agonists, and especially sodium-glucose cotransporter-2 inhibitors) have been shown to attenuate the inflammatory response or expansion of EAT. Importantly, these treatments may be beneficial in improving the clinical symptoms or prognosis of patients with HFpEF. Accordingly, well-designed randomized controlled trials are needed to validate the efficacy of current therapies. In addition, more novel and effective therapies targeting EAT are needed in the future.

Key Words: Epicardial adipose tissue; Heart failure with preserved ejection fraction; Type 2 diabetes mellitus; Inflammation; Anti-hyperglycemic drugs; Sodium-glucose

cotransporter-2 inhibitors

Core Tip: Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome requiring individualized treatment depending on phenotypic differences. HFpEF with type 2 diabetes mellitus is strongly associated with the expansion, inflammation, and hypermetabolic activity of epicardial adipose tissue (EAT). Thus, targeting EAT may be a promising therapeutic strategy for HFpEF with type 2 diabetes mellitus. Lifestyle management, bariatric surgery, and certain drugs may suppress the accumulation of EAT and improve the clinical symptoms and prognosis of HFpEF. More studies are required to validate the efficacy of current treatments and to develop new effective therapies.

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INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF), a systemic and heterogeneous syndrome, is characterized by various comorbidities (mainly diabetes mellitus, hypertension, and metabolic syndrome), multiple cardiac and extracardiac pathophysiologic abnormalities, and diverse phenotypic presentations[1]. HFpEF is a growing public health challenge, which currently accounts for approximately half of HF cases, and its prevalence continues to rise due to an aging population and the increasing burden of comorbidities[2]. Additionally, HFpEF is associated with poor prognosis, with a 5-year mortality rate of up to 75%[3]. Standardized and effective interventions are lacking due to the complex pathophysiological underpinnings and clinical heterogeneity of HFpEF[4]. It may, however, be beneficial to halt disease progression and thus improve prognosis by providing individualized treatment based on phenotypic differences[4].

Type 2 diabetes mellitus (T2DM) is a substantial risk factor for the emergence and progression of HFpEF, and approximately 45%-50% of HFpEF cases suffer from T2DM, a specific phenotype of HFpEF [5,6]. Systemic inflammation related to glucose metabolism disorders is accepted as a critical pathological mechanism of HFpEF with T2DM, which is responsible for the expansion and dysfunction (inflammation and hypermetabolic activity) of epicardial adipose tissue (EAT)[7]. EAT, a metabolically active visceral fat depot, can regulate the pathophysiological processes of HFpEF with T2DM through the paracrine and endocrine mechanisms[8]. Thus, inhibiting the accumulation of EAT may be a promising therapeutic strategy for HFpEF with T2DM. At present, lifestyle management, bariatric surgery, and some medications may contribute to reducing the inflammation response or accumulation of EAT, despite the fact that there is no available treatment for EAT. Notably, these interventions may attenuate pathological changes and improve the prognosis in patients with HFpEF.

Currently, a comprehensive review is lacking discussing the pathogenesis of EAT-mediated HFpEF with T2DM and therapies to inhibit EAT expansion. In this review, we evaluated the role of EAT in the development of HFpEF with T2DM and discussed current therapies to attenuate EAT expansion as well as future therapeutic perspectives.

ANATOMY, PATHOLOGY AND PATHOPHYSIOLOGY OF EAT

Anatomy of EAT

EAT represents the local visceral fat depot of the heart, located between the myocardium and the visceral pericardium[9] (Figure 1). Under healthy circumstances, EAT accounts for approximately 20% of the total heart weight and covers 80% of the cardiac surface[10,11]. In adults, EAT typically surrounds the coronary arteries and their major epicardial branches, mainly concentrated in the interventricular and atrioventricular grooves, with lesser amounts covering the atria, the free wall of the right ventricle, and the apex[9]. Interestingly, EAT is anatomically and functionally contiguous with the myocardium because of the shared microcirculation and the absence of muscle fascia, which may facilitate the local interaction of EAT with the myocardium and coronary arteries through vasocrine or paracrine cross-talk [12]. Microscopically, EAT consists typically of adipocytes specialized in energy storage but also includes inflammatory cells (mainly macrophages and mast cells), immune cells, stromovascular cells,

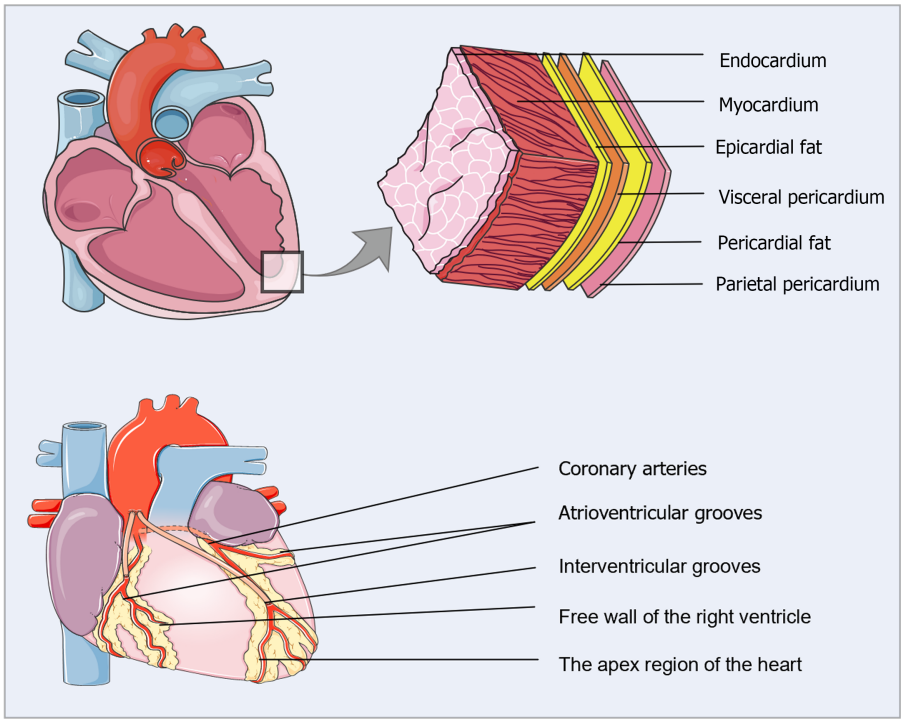

Figure 1 Anatomical location of epicardial adipose tissue. Epicardial adipose tissue (EAT) is situated between the myocardium and the visceral pericardium. In normal adults, EAT usually accompanies the coronary arteries and their major epicardial branches, mainly concentrated in the interventricular and atrioventricular grooves, with lesser amounts covering the atria, the free wall of the right ventricle, and the apex.

and ganglia in normal adults. In pathological states, however, numerous inflammatory cell aggregates and abnormal expansion of the microvascular network are present in the EAT[13].

Physiology of EAT

EAT acts as a shock absorber, protecting coronary arteries from excessive distortion and compression during the contraction of the adjacent myocardium[14]. EAT has a greater capacity to release and uptake free fatty acids (FFA) compared to other visceral fat depots. The myocardium metabolizes FFAs from the coronary arterial blood, which is shared with the contiguous EAT. FFA oxidation is responsible for almost 50%-70% of the energy production in the heart[15]. Accordingly, EAT might serve as a physiological buffer to protect the myocardium from excessive fatty acid levels and as a direct energy source to provide FFA under increased metabolic demand. Moreover, EAT expresses uncoupling protein-1 (UCP1), a thermogenic protein located in the inner membrane of mitochondria. UCP1 uncouples oxidative phosphorylation from ATP synthesis, ultimately dissipating energy as heat[16]. EAT might, therefore, provide direct heat to the myocardium and protect the heart under unfavorable hemodynamic conditions.

Pathophysiology of EAT

EAT has been widely established as a remarkably active endocrine organ that secretes various bioactive molecules, such as cytokines, adipokines, and chemokines, that can exert protective or detrimental effects depending on the local microenvironmental situation[17]. EAT can, therefore, locally modulate the adjacent myocardium and coronary arteries through the vasocrine or paracrine secretion of these bioactive molecules[12]. Physiologically, EAT mainly releases anti-inflammatory adipocytokines, such as adiponectin, adrenomedullin, omentin, and interleukin-10 (IL-10), which contribute to cardioprotection and anti-atherosclerosis[14]. In contrast, adipocytes enlarge and produce high quantities of FFAs under pathological conditions, triggering EAT expansion, localized hypoxia, and the infiltration of macrophages, ultimately resulting in a chronic inflammatory response[8]. Subsequently, numerous proinflammatory adipokines are produced and accumulated, including IL-6, tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein-1, leptin, resistin, and serglycin, which aggravate local inflammation, thereby affecting the heart and coronary arteries[12].

CONTRIBUTIONS OF EAT TO HFPEF WITH T2DM

EAT in the pathophysiology of HFpEF with T2DM

Dysregulated glucose metabolism is a fundamental clinical characteristic of T2DM and is strongly connected with the aberrant accumulation of EAT[18-20]. As reported in Table 1, EAT thickness over the right ventricular free wall, EAT volume, or EAT area were significantly higher in patients with impaired fasting glucose, insulin resistance, or T2DM than in control subjects[21-39]. A meta-analysis of nine studies by Li *et al*[40] confirmed a positive correlation between the presence of T2DM and EAT expansion. Eventually, increased EAT deposition interacts directly with the heart through mechanical and metabolic mechanisms, leading to myocardial fibrosis, cardiomyocyte stiffness, and left ventricular (LV) diastolic dysfunction, which are the essential pathological features of HFpEF (Figure 2).

In terms of machinery, increased EAT occupies a large space in the cardiac fossa and applies a compressive contact force on the heart, resulting in pericardial restrain, increased ventricular filling pressures, and LV diastolic dysfunction. A meta-analysis of 11 studies showed that increasing EAT was independently associated with LV diastolic dysfunction even after adjusting for age, sex, and measures of adiposity[41]. In patients with T2DM, Christensen *et al*[27] and Song *et al*[42] substantiated the deleterious effect of increased EAT on LV global longitudinal strain and LV diastolic function assessed by peak velocity during early diastole (E)/peak velocity during atrial contraction (A) ratio, early diastolic mitral annular velocity (e'), and E/e' ratio.

In terms of metabolism, EAT enlargement is linked to the buildup of FFAs and lipid metabolites[43], which induce myocardial lipotoxicity and in turn contribute to excessive oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction, ultimately causing LV diastolic dysfunction[44]. Furthermore, excessive cardiomyocyte lipid deposits may lead to cardiac steatosis, which has been demonstrated to be an early marker of diabetic heart disease and is independently associated with LV diastolic function[45-47]. Simultaneously, hypertrophic adipocytes and activated macrophages exhibit increased production of proinflammatory adipocytokines and chemokines in EAT. These proinflammatory factors cause local inflammation, excessive oxidative stress, microvascular and endothelial dysfunction, and extracellular matrix deposition through vasocrine or paracrine mechanisms, resulting in cardiomyocyte stiffness, myocardial fibrosis, and subsequent LV diastolic dysfunction[8,9].

Relationship between increased EAT and clinical characteristics of HFpEF

As shown in Table 2, EAT expansion is closely related to severe pathologic changes, clinical manifestations, and long-term prognosis in individuals with HFpEF[48-55]. According to research by van Woerden *et al*[48] and Pugliese *et al*[54], enlarged EAT is linked to increased plasma myocardial injury markers. Wang *et al*[49] found that the EAT volume was positively correlated with elevated inflammatory markers (C-reactive protein), LV hypertrophy (LV mass index), and LV diastolic dysfunction (E/e' ratio and tricuspid regurgitation velocity). Venkateshvaran *et al*[50] confirmed that higher EAT was linked not only to LV hypertrophy and diastolic dysfunction but also to endothelial dysfunction. Koepp *et al*[51] showed that thickened EAT was associated with elevated cardiac filling pressures, pulmonary hypertension, and pericardial constraint. Additionally, some studies have confirmed that increased EAT may lead to decreased exercise tolerance or quality of life[50-54]. Importantly, EAT thickening was correlated with a 1.12-fold increased risk of the composite endpoint of death and HF hospitalization after 21 mo of follow-up, according to Pugliese *et al*[54]. After 24 mo of follow-up, van Woerden *et al*[55] confirmed that EAT expansion increased the risk of all-cause mortality, HF hospitalization, and the composite endpoint.

CURRENT INTERVENTIONS TARGETING EAT AND FUTURE THERAPEUTIC PERSPECTIVES IN HFPEF WITH T2DM

EAT plays an important role in the development and progression of HFpEF with T2DM and is strongly associated with an increased risk of adverse outcomes. Therefore, alleviating EAT expansion may be a promising therapeutic strategy. Although no treatment is available specifically for EAT, lifestyle management, bariatric surgery, and medications (Table 3) including anti-hyperlipidemia, anti-cytokines, and anti-hyperglycemia have been demonstrated to reduce the inflammation response or expansion of EAT and appear to be beneficial for HFpEF (Figure 3).

Non-pharmacological interventions

In diabetic and obese patients, lifestyle modifications (including a low-calorie diet and exercise training) and bariatric surgery can reduce EAT levels. Twenty severely obese patients were shown to have a 32% reduction in EAT thickness and alleviation in LV hypertrophy and diastolic dysfunction after 6 mo of calorie restriction with moderate exercise[56]. Serrano-Ferrer *et al*[57] confirmed that exercise training significantly reduced EAT thickness and serum TNF-α, increased lipocalin, and improved LV myocardial strain and strain rate. A study by Honkala *et al*[58] reported that 2 wk of continuous exercise

Table 1 Epicardial adipose tissue expansion in patients with glucose metabolism disorders

Ref.	Participants, *n*	Amount of EAT in the observation group	Amount of EAT in the control group	*P* value
EAT thickness (mm) measured by echocardiography thickness on the right ventricular free wall				
Baloglu *et al*[21], 2019	T2DM patients: 128; healthy controls: 32	3.53 ± 0.79	4.64 ± 1.39	< 0.001
Akbas *et al*[22], 2014	T2DM patients: 156; healthy controls: 50	4.66 ± 1.50	3.91 ± 1.60	0.005
Chen *et al*[23], 2017	T2DM patients: 167; healthy controls: 82	4.00 (3.00-5.00)	2.00 (1.00-3.00)	< 0.001
Philouze *et al*[24], 2017	T2DM patients: 44; healthy controls: 35	6.40 ± 1.70	3.30 ± 1.10	< 0.001
Cetin *et al*[25], 2013	T2DM patients: 139; age- and sex-matched controls: 40	6.00 ± 1.50	4.42 ± 1.00	< 0.001
Yafei *et al*[26], 2019	T2DM patients: 76; age- and sex-matched controls: 30	6.23 ± 1.27	4.60 ± 1.03	< 0.001
Christensen *et al*[27], 2019	T2DM patients: 770; age- and sex-matched controls: 234	4.60 ± 1.80	3.40 ± 1.20	< 0.0001
Wang *et al*[28], 2017	T2DM with duration ≤ 10 yr: 35; T2DM with duration > 10 yr: 33	4.47 ± 1.90	5.45 ± 1.40	< 0.05
Altin *et al*[29], 2016	Patients with IR: 113; age- and sex-matched controls: 112	7.34 ± 1.96	5.22 ± 1.75	< 0.001
Iacobellis *et al*[30], 2008	Patients with IFG: 65; non-diabetic controls: 50	Males: 8.00 ± 3.00	6.00 ± 2.00	< 0.001
		Females: 7.10 ± 4.00	5.80 ± 3.00	
EAT volume (cm^3) measured by computed tomography				
Wang *et al*[31], 2008	T2DM patients: 49; non-diabetic controls: 78	166.1 ± 60.6	123.4 ± 41.8	< 0.0001
Akyürek *et al*[32], 2014	T2DM patients: 93; non-diabetic controls: 85	40.1 ± 23.9	16.9 ± 7.7	< 0.001
Gullaksen *et al*[33], 2019	T2DM patients: 44; non-diabetic controls: 59	119.0 ± 49.0	86.0 ± 40.0	< 0.001
Groves *et al*[34], 2014	T2DM patients: 92; non-diabetic controls: 59	118.6 ± 43.0	70.0 ± 44.0	< 0.0001
Versteylen *et al*[35], 2012	Patients with IFG: 118; non-diabetic controls: 209	92.0 ± 39.0	75.0 ± 34.0	< 0.001
EAT volume (cm^3) or area (cm^2) measured by cardiac magnetic resonance				
Huang *et al*[36], 2022	T2DM with duration ≤ 5 yr: 56; T2DM with duration > 5 yr: 57	48.4 ± 13.4 cm^3	58.4 ± 17.3 cm^3	< 0.001
Evin *et al*[37], 2016	T2DM patients: 20; healthy controls: 19	135.0 ± 31.0 cm^3	90.0 ± 30.0 cm^3	< 0.001
Al-Talabany *et al*[38], 2018	T2DM patients: 54; non-diabetic controls: 29	13.5 ± 3.5 cm^2	11.8 ± 4.1 cm^2	< 0.05
Rado *et al*[39], 2019	Prediabetes patients: 100; healthy controls: 200	9.2 cm^2	7.7 cm^2	< 0.001

EAT: Epicardial adipose tissue; IFG: Impaired fasting glucose; IR: Insulin resistance; T2DM: Type 2 diabetes mellitus.

training resulted in decreased EAT volume and myocardial triglyceride levels and improved aerobic exercise tolerance and insulin sensitivity in 16 patients with T2DM. A meta-analysis including five studies confirmed that exercise training reduced epicardial fat deposition[59].

Several studies have reported that bariatric surgery substantially reduces the accumulation of EAT in patients[60-64]. Gaborit *et al*[62] found a 27% reduction in EAT volume in obese patients at a 6-mo follow-up after bariatric surgery. In addition, individuals with HFpEF appear to benefit from lifestyle changes and bariatric surgery in terms of improved microvascular and endothelial dysfunction, left ventricular remodeling and diastolic dysfunction, exercise tolerance, and quality of life[65-68]. Thus, lifestyle modification and bariatric surgery may alleviate the abnormal expansion of EAT in HFpEF patients with obesity and T2DM and improve LV diastolic function and clinical symptoms. Nevertheless, further research is required to determine whether it can improve the prognosis of patients.

Table 2 Relationship between increased epicardial adipose tissue and clinical characteristics of heart failure with preserved ejection fraction

Ref.	Participants, *n*	Imaging method	Relationship between increased EAT and clinical characteristics of HFpEF		
			Pathological changes	Clinical manifestations	Prognosis
van Woerden *et al* [48], 2018	64 HF patients with LVEF > 40%	CMR	Myocardial injury: increased creatine kinase-MB and TnT	Decreased quality of life (KCCQ score)	
Wang *et al*[49], 2022	53 HF patients with LVEF > 50%	CMR	Inflammation: increased CRP; LV hypertrophy: increased LVmass index; LV diastolic dysfunction: increased E/e' and tricuspid regurgitation velocity		
Venkateshvaran *et al* [50], 2022	182 HF patients with LVEF > 50%	Echo	Inflammation; endothelial dysfunction; LV hypertrophy: increased LV septal wall thickness; LV diastolic dysfunction: increased E peak deceleration time	Decreased quality of life (KCCQ score)	
Koepp *et al*[51], 2020	169 HF patients with LVEF > 50%	Echo	Increased cardiac filling pressures, pulmonary hypertension, and pericardial restraint	Decreased exercise capacity (VO_2, AVO_2 diff)	
Haykowsky *et al* [52], 2018	100 HF patients with LVEF > 50%	CMR		Decreased exercise capacity (VO_2, 6-min walk test, leg power)	
Gorter *et al*[53], 2020	75 HF patients with LVEF > 45%	Echo		Decreased exercise capacity (VO_2)	
Pugliese *et al*[54], 2021	188 HF patients with LVEF > 50%	Echo	Myocardial injury: increased TnT; inflammation: increased CRP	Decreased exercise capacity (peak VO_2 and AVO_2 diff)	Increased risk of the composite endpoint of HF hospitalization and cardiovascular deaths
van Woerden *et al* [55], 2022	105 HF patients with LVEF > 40%	CMR			Increased risk of HF hospitalization, all-cause death, and the composite endpoint

AVO_2 diff: Non-invasive arterial-venous oxygen content difference; CMR: Cardiac magnetic resonance; CRP: C-reactive protein; EAT: Epicardial adipose tissue; Echo: Echocardiography; E/e': Peak velocity during early diastole/early diastolic mitral annular velocity; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; KCCQ: Kansas City cardiomyopathy questionnaire; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MB: Myocardial band; TnT: Troponin T; VO_2: Peak oxygen consumption.

Pharmacological interventions

Anti-cytokine drugs: Inflammation is an essential driver of abnormal EAT expansion. Theoretically, anti-cytokine drugs (anti-IL-1 and anti-IL-6, *etc*) can interfere with the pathophysiological process of EAT expansion and may eventually decrease EAT accumulation. Unfortunately, there are no relevant studies to confirm this. Furthermore, anti-cytokine drugs, particularly IL-1 blockade, have shown cardioprotective effects in many cardiovascular diseases[69]. Nevertheless, few clinical studies have examined their effects on HFpEF, and the results are inconsistent. The D-HART trial showed that a 14-d intervention with anakinra, an IL-1 blocker, significantly reduced the systemic inflammatory response and improved aerobic exercise capacity in individuals with HFpEF (n = 12)[70]. Contrarily, the D-HART 2 trial found that anakinra intervention for 12 d failed to improve exercise capacity in patients with HFpEF (n = 21)[71]. Therefore, whether anti-cytokine drugs reduce EAT deposition has not been confirmed in clinical investigations, and their role in HFpEF with T2DM requires validation in standardized randomized controlled trials.

Anti-hyperlipidemic drugs: Statins are 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors that can significantly reduce endogenous cholesterol production by inhibiting the rate-limiting enzyme in cholesterol synthesis[72]. As the anti-inflammatory effects have been established, researchers have begun to explore the role of statins in EAT in the last decade. According to Parisi *et al*[73], statin therapy dramatically decreased EAT thickness and EAT-secreted inflammatory mediators in individuals with aortic stenosis. In patients who successfully underwent percutaneous coronary intervention, Park *et al* [74] demonstrated that atorvastatin (20 mg/d) reduced EAT thickness more significantly than simvastatin/ezetimibe (10/10 mg/d). Soucek *et al*[75] confirmed that substantial reductions in EAT were associated with intensive atorvastatin therapy (80 mg/d) in atrial fibrillation patients undergoing pulmonary vein isolation. A study by Alexopoulos *et al*[76] showed that intensive treatment (atorvastatin, 80 mg/d) was more successful in inducing EAT reduction than moderate-intensity treatment

Table 3 Pharmacological interventions targeting epicardial adipose tissue

Ref.	Imaging method	Participants, *n*	Intervention method and duration	Change of EAT	Other findings
Park *et al*[74], 2010	Echo	145 coronary artery stenosis patients	Atorvastatin: *n* = 82, 20 mg/d; simvastatin: *n* = 63, 10 mg/d; for 6-8 mo	Atorvastatin decreased EAT thickness (0.47 ± 0.65 mm) more than simvastatin (EAT 0.12 ± 0.52 mm, *P* = 0.001)	Decreased TC, TG, and LDL-C
Soucek *et al* [75], 2015	CT	38 atrial fibrillation patients	Atorvastatin: 80 mg/d, for 3 mo	EAT volume decreased from 86.9 (64.1-124.8) mL to 92.3 (62.0- 133.3) mL (*P* < 0.05)	Decreased CRP, TC, and LDL-C
Alexopoulos *et al*[76], 2013	CT	420 hyperlipidemic post-menopausal women	Atorvastatin: *n* = 194, 80 mg/d; pravastatin: *n* = 226, 40 mg/d; for 12 mo	Atorvastatin decreased EAT volume (3.38%) more than pravastatin (0.83%, *P* = 0.025)	Decreased TC, TG, and LDL-C
Rivas Galvez *et al*[78], 2020	Echo	41 patients treated with PCSK9 inhibitors	Evolocumab: *n* = 16; alirocumab: *n* = 8; twice in 6 mo	EAT thickness decreased by 20.39% (*P* = 0.0001).	Decreased BMI, TC, and LDL-C
Iacobellis *et al* [82], 2017	Echo	41 patients T2DM	Metformin: 500 mg-1000 mg, twice daily, for 6 mo	EAT thickness changed from 7.4 ± 1.6 mm to 7.5 ± 1.5 mm and 6.9 ± 1.3 mm at 3 and 6 mo, respectively	Decreased BMI
Ziyrek *et al* [83], 2019	Echo	40 T2DM patients	Metformin: 1000 mg, twice daily, for 3 mo	EAT thickness decreased from 5.07 ± 1.33 mm to 4.76 ± 1.32 mm (*P* < 0.001)	
Iacobellis *et al* [84], 2020	Echo	51 T2DM patients	Metformin: 500 mg-1000 mg, twice daily, for 6 mo	EAT thickness decreased from 8.0 ± 2.5 mm to 7.4 ± 2.5 mm and 7.5 ± 2.4 mm at 3 and 6 mo, respectively (compared with baseline *P* < 0.016)	
Moody *et al* [90], 2014	CMR	12 T2DM patients	Pioglitazone: 15 mg/d, for 2 wk, then increase to 45 mg/d, for 22 wk	EAT area decreased from 15.3 ± 3.9 cm^2 to 14.0 ± 3.9 cm^2 (*P* = 0.03)	Decreased paracardial adipose tissue; improved left ventricular diastolic function
Lima-Martínez *et al*[94], 2015	Echo	26 T2DM patients	Combination of sitagliptin (50 mg) and metformin (1000 mg), twice daily, for 24 wk	EAT thickness reduction of 15% (*P* = 0.001)	
van Eyk *et al* [99], 2019	CMR	22 T2DM patients	Liraglutide: 0.6 mg/d gradually increased to 1.8 mg/d in 2 wk, for 26 wk	EAT area reduction of 0 ± 2 cm^2	Decreased visceral fat volume
Bizino *et al* [100], 2020	CMR	23 T2DM patients	Liraglutide: 0.6 mg/d gradually increased to 1.8 mg/d in 2 wk, 26 wk	EAT area reduction of 1.1 ± 6.0 cm^2	Decreased body weight and subcutaneous fat
Iacobellis *et al* [82], 2017	Echo	54 T2DM patients	Combination of liraglutide (increased to 1.8 mg/once daily) and metformin (1000 mg, twice daily), for 12 wk	EAT thickness reduction of 29% and 36% at 3 and 6 mo, respectively	Decreased BMI and HbA1c
Zhao *et al* [101], 2021	Echo	21 T2DM patients	Liraglutide: 0.6 mg/d gradually increased to 1.2 mg/d in 3-5 d, for 3 mo	EAT decreased from 5.00 (5.0-7.0) mm to 3.95 ± 1.43 mm (*P* < 0.001)	Decreased weight, HbA1c, TC, TG, and LDL-C
Dutour *et al* [102], 2016	CMR	22 T2DM patients	Exenatide: 5 mg twice daily, for 4 wk, then increase to 10 mg twice daily, for 22 wk	EAT volume reduction of 8.8 ± 2.1%	Decreased weight, HbA1c, and hepatic triglyceride content
Morano *et al* [103], 2015	Echo	25 T2DM patients	Combination of exenatide (5 mg twice daily, for 1 mo, and then increase to 10 mg twice daily, for 2 mo) and liraglutide (1.2 mg/d), for 3 mo	EAT thickness decreased from 9.4 ± 1.6 mm to 8.0 ± 1.9 mm (*P* = 0.003)	Decreased MRI; improved renal resistive index
Iacobellis *et al* [104], 2020	Echo	6 T2DM patients	Semaglutide: *n* = 30, 1 mg weekly; dulaglutide: *n* = 30, 1.5 mg weekly; for 12 wk	EAT thickness reduction of 20% in both semaglutide and dulaglutide groups	Decreased BMI and HbA1c
Requena *et al* [108], 2021	CMR	84 non-diabetic patients with HFrEF	Empagliflozin: 10 mg/d, for 6 mo	EAT volume reduction of 5.14 mL, *P* < 0.05	Decreasing subcutaneous fat and matrix volume
Ardahanlı *et al* [109], 2021	Echo	37 T2DM patients	Empagliflozin: 10 mg/d, for 6 mo	EAT thickness decreased from 7.6 ± 1.7 mm to 6.7 ± 1.3 mm (*P*	Decreased BMI, waist circumference, HbA1c, uric acid,

				< 0.001)	systolic and diastolic blood pressure, and carotid intima-media thickness
Iacobellis *et al* [84], 2020	Echo	51 T2DM patients	Combination of dapagliflozin (5 to 10 mg/d) and metformin (500 to 1000 mg, twice daily), for 24 mo	EAT thickness decreased by 15% from baseline to 12 wk and 20% after 24 wk (compared with baseline $P < 0.01$)	Decreased weight and HbA1c
Sato *et al*[110], 2018	CT	20 T2DM patients	Dapagliflozin: 10 mg/d, for 6 mo	EAT volume reduction of 16.4 ± 8.3 mL ($P < 0.05$)	Decreased HbA1c, TNF-α, TG, insulin resistance, and left atrial dimension
Sato *et al*[111], 2020	CT	18 T2DM patients with coronary artery disease	Dapagliflozin: 5 mg/d, for 6 mo	EAT volume reduction of 15.2 ± 12.8 mL ($P < 0.05$)	Decreased HbA1c, TNF-α, and insulin resistance
Braha *et al* [112], 2021	CT	52 T2DM patients	Dapagliflozin: 10 mg/d, for 6 mo	EAT volume reduction of 17.1% ($P < 0.001$)	Decreased BMI, triglyceride glucose index, and HbA1c
Yagi *et al*[113], 2017	Echo	13 T2DM patients	Canagliflozin: 100 mg/d, for 6 mo	EAT thickness decreased from 9.3 ± 2.5 to 8.1 ± 2.3 mm ($P < 0.01$) and to 7.3 ± 2.0 mm ($P < 0.001$) at 3 mo and 6 mo, respectively	Decreased BMI
Fukuda *et al* [114], 2017	CMR	9 T2DM patients	Ipragliflozin: 50 mg/d, 12 wk	EAT volume decreased from 102 (79-126) mL to 89 (66-109) mL ($P = 0.008$)	Decreased weight, BMI, HbA1c, TG, leptin, fasting plasma glucose, and insulin resistance
Bouchi *et al* [115], 2017	CMR	19 T2DM patients	Luseogliflozin: 2.5-5.0 mg/d for 12 wk	EAT volume decreased from 117 (96-136) mL to 111 (88-134) mL ($P = 0.048$)	Decreased weight, BMI, systolic and diastolic blood pressure, HbA1c, fasting plasma glucose, insulin resistance, and CRP
Gaborit *et al* [116], 2021	CMR	26 T2DM patients	Empagliflozin: 10 mg/d, 12 wk	EAT volume decreased from 108.5 ± 31.8 mL to 106.9 ± 31.8 mL ($P = 0.09$)	Decreased BMI, TG, HbA1c, fasting blood glucose, liver fat content, and visceral fat volume

BMI: Body mass index; CMR: Cardiovascular magnetic resonance; CRP: C-reactive protein; CT: Computed tomography; EAT: Epicardial adipose tissue; Echo: Echocardiography; HbA1c: Glycosylated hemoglobin; HFrEF: Heart failure with reduced ejection fraction; LDL-C: Low-density lipoprotein cholesterol; MRI: Magnetic resonance imaging; PCSK9: Proprotein convertase subtilisin/kexin type 9; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; TNF-α: Tumor necrosis factor-α.

(pravastatin, 40 mg/d) in hyperlipidemic post-menopausal women.

Furthermore, proprotein convertase subtilisin/kexin type 9 (PCSK9), part of the EAT secretome, is involved in EAT-induced inflammation[77]. Therefore, PCSK9 inhibitors, a new class of lipid-lowering drugs, may inhibit the abnormal expansion of EAT. A non-randomized cohort of 24 patients reported a 20.39% reduction in EAT thickness after 6 mo of PCSK9 inhibitor treatment (evolocumab or alirocumab) [78]. In recent years, statin therapy has been reported to considerably reduce mortality in patients with HFpEF, possibly associated with a reduction in the inflammatory response or accumulation of EAT[79, 80]. Thus, hypolipidemic medicines may attenuate aberrant EAT expansion and be advantageous in diabetic HFpEF, and well-designed randomized controlled trials are still needed to validate this.

Anti-hyperglycemic drugs: Metformin, an oral anti-hyperglycemic drug for patients with T2DM, lowers blood glucose levels by decreasing hepatic glucose production (gluconeogenesis) and improves insulin sensitivity by increasing peripheral glucose uptake and utilization[81]. In recent years, several studies have begun to explore its impacts on EAT, as its positive effects on reducing body weight and fat composition have been revealed. Iacobellis *et al*[82] showed that metformin treatment (500-1000 mg, twice daily) for 3-6 mo failed to reduce EAT thickness in patients with T2DM. In contrast, Ziyrek *et al* [83] found a significant reduction of EAT thickness after 3 mo of metformin monotherapy (1000 mg, twice daily) in individuals with T2DM. After increasing the sample size, Iacobellis *et al*[84] also discovered that metformin slightly reduced EAT thickness. Additionally, metformin treatment decreased mortality in HFpEF patients and improved LV hypertrophy and diastolic dysfunction[85,86]. Unfortunately, studies on the effects of metformin on EAT accumulation are scarce and controversial, and future research is needed to generate robust evidence.

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists, can enhance insulin sensitivity by activating peroxisome proliferator-activated receptor gamma[87]. As a result, it reduces the secretion of proinflammatory cytokines in the visceral fat depots and thereby can inhibit the abnormal enlargement of EAT[88]. Pioglitazone, a member of TZDs, was shown to significantly reduce EAT inflammatory markers (IL-6, TNF-α, resistin, and matrix metalloproteinase-9) and increase adiponectin in patients with coronary artery disease and metabolic syndrome

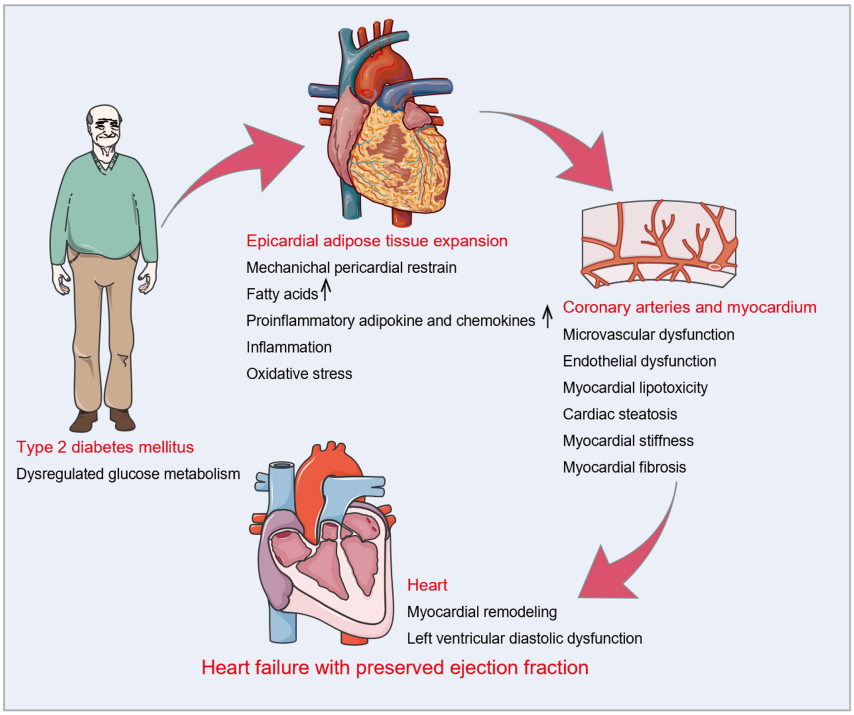

Figure 2 Epicardial adipose tissue in the pathophysiology of heart failure with preserved ejection fraction with type 2 diabetes mellitus. Dysregulated glucose metabolism is intimately related to the expansion of epicardial adipose tissue (EAT). Increased EAT deposition interacts directly with the heart through mechanical and metabolic mechanisms. Mechanically, EAT expansion may directly contribute to pericardial restrain, resulting in left ventricular (LV) diastolic dysfunction. Metabolically, EAT enlargement is linked to the buildup of free fatty acids, which may induce myocardial lipotoxicity and cardiac steatosis. Simultaneously, hypertrophic adipocytes and activated macrophages secrete numerous proinflammatory adipocytokines and chemokines in EAT. Subsequent local inflammation, excessive oxidative stress, microvascular and endothelial dysfunction, and myocardial stiffness and fibrosis ultimately lead to LV remodeling and diastolic dysfunction.

[89]. According to Moody *et al*[90], pioglitazone treatment was linked to a 9% reduction in EAT area and improvement in LV diastolic function in patients with T2DM, and there was a significant negative correlation between EAT and LV diastolic function. However, TZDs may cause serious cardiovascular adverse effects, especially HF[91,92]. As a result, the clinical use of TZDs in the treatment of HFpEF is limited due to their potential to exacerbate HF.

Dipeptidyl peptidase 4 (DPP-4) inhibitors improve glucose-dependent insulin secretion by increasing bioactive incretins, which inhibit glucagon release and then promote insulin production to decrease blood glucose levels[93]. Only a single-group pre-post study by Lima-Martínez *et al*[94] showed that 26 overweight patients with T2DM had a 15% reduction in EAT thickness after 6 mo of treatment with a combination of metformin and sitagliptin, a DPP-4 inhibitor. Unfortunately, there is a lack of research on regulating EAT using DPP-4 inhibitors alone. Therefore, relevant studies still need to support whether DPP-4 inhibitors can reduce EAT accumulation. In addition, it is controversial whether an increased risk of HF is associated with DPP-4 inhibitors[95].

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) comprise a novel anti-diabetic drug class that maintains glucose homeostasis by stimulating glucose-dependent insulin secretion, suppressing glucagon release, and inhibiting gastric emptying[96]. Previous studies reported the presence of GLP-1R in EAT with mRNA and protein expression, and targeting GLP-1R in EAT can reduce local adipogenesis, enhance fat utilization, and drive brown fat differentiation[97,98]. According to research by van Eyk *et al*[99] and Bizino *et al*[100], liraglutide reduced visceral or subcutaneous fat but failed to reduce EAT accumulation in T2DM. Five investigations, however, demonstrated that liraglutide[82,101-103], exenatide[102,103], semaglutide[104], and dulaglutide[104] not only significantly decreased EAT deposition but also improved glycolipid metabolism disorders. A meta-analysis performed by Berg *et al*[105] confirmed that GLP1-RAs suppressed the abnormal accumulation of EAT. Moreover, liraglutide treatment has been shown to improve LV stiffness and diastolic dysfunction and reduce mortality in HFpEF patients[106]. As a result, GLP1-RAs can inhibit abnormal EAT expansion and may be beneficial for HFpEF. However, further research on this subject is still necessary due to the small numbers of both studies and subjects.

Sodium-glucose cotransporter 2 inhibitors (SGLT2-Is), the newly developed anti-hyperglycemic agents, bind to the SGLT2 transporter in the proximal tubule of the kidney and then promote the urinary excretion of glucose by preventing the reabsorption of glucose[96]. In recent years, SGLT2-Is have been found to play an essential role in mediating anti-inflammatory effects, and therefore its role in regulating EAT has gained significant attention. In individuals undergoing cardiac surgery, Diaz Dí

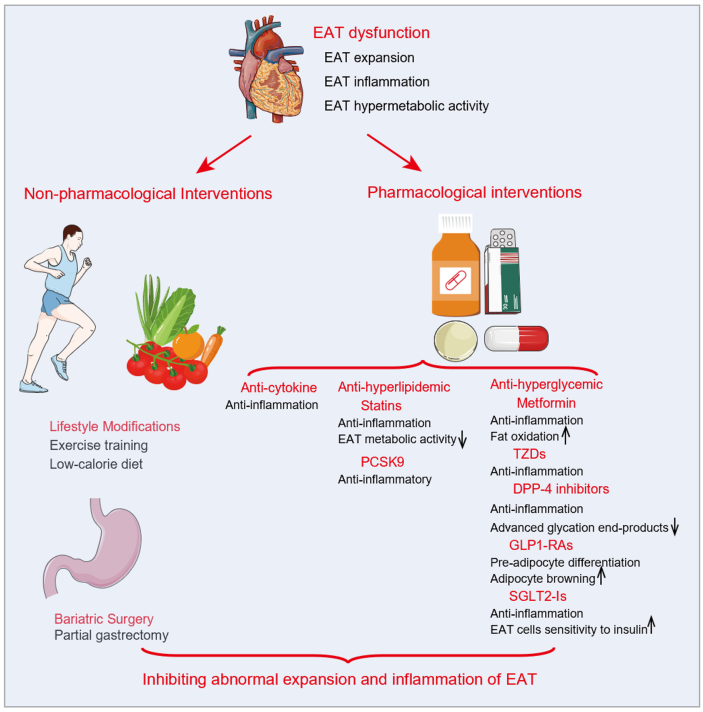

Figure 3 Current interventions targeting epicardial adipose tissue and possible mechanisms. Current interventions targeting epicardial adipose tissue (EAT) reported in the literature include non-pharmacological interventions (lifestyle management and bariatric surgery) and pharmacological interventions related to anti-cytokines, anti-hyperlipidemia, and anti-hyperglycemia. By increasing fat oxidation or sensitivity to insulin and inhibiting inflammation or hypermetabolic activity, these interventions may prevent abnormal expansion and inflammation of EAT. EAT: Epicardial adipose tissue; DPP-4: Dipeptidyl peptidase 4; GLP1-RAs: Glucagon-like peptide-1 receptor agonists; PCSK9: Proprotein convertase subtilisin/kexin type 9; SGLT2-Is: Sodium-glucose cotransporter 2 inhibitors; TZDs: Thiazolidinediones.

az-Rodríguez *et al*[107] demonstrated the expression of SGLT2 in EAT and that dapagliflozin promoted the differentiation of EAT cells and decreased the release of proinflammatory chemokines in *in vitro* assays. Multiple clinical studies have demonstrated that SGLT2-Is (empagliflozin[108,109], dapagliflozin [84,110-112], canagliflozin[113], ipragliflozin[114], luseogliflozin[115]) can dramatically decrease EAT deposition, improve glucolipid metabolism, and reduce inflammatory responses. Conversely, only one study by Gaborit *et al*[116] indicated that empagliflozin failed to reduce EAT volume in patients with T2DM.

A meta-analysis conducted by Masson *et al*[117] confirmed that SGLT2-Is could significantly reduce EAT accumulation and improve glucolipid metabolism. Interestingly, Requena-Ibáñez *et al*[108] reported that empagliflozin could reduce EAT volume in patients with non-diabetic HFrEF. According to Yagi *et al*[113], canagliflozin reduced EAT thickness independent of lowering blood glucose. Thus, SGLT2-Is play an essential role in inhibiting EAT accumulation, possibly independent of glycemic control. Moreover, the current studies confirmed that SGLT2-Is exerts direct pleiotropic effects on the myocardium of HFpEF model animals through multiple mechanisms, such as reducing inflammation, suppressing oxidative stress, and improving cardiac structural and functional dysfunction (myocardial hypertrophy, stiffness fibrosis, and LV diastolic dysfunction)[118-121]. Clinically, SGLT2-Is (empagliflozin and dapagliflozin) have been confirmed to improve exercise tolerance[122] and quality of life in HFpEF patients[123,124] and lower the risk of cardiovascular death or HF hospitalization[125-127]. Consequently, SGLT2-Is exhibit significant prevention of abnormal EAT expansion and positive therapeutic effects in HFpEF, which warrants further clinical validation.

SUMMARY AND FUTURE PERSPECTIVES

T2DM can be one of the essential drivers of the occurrence and development of HFpEF and is associated with a worse prognosis of HFpEF. Systemic inflammation associated with glucose metabolism disorders is a crucial pathological mechanism for HFpEF with T2DM, which is associated with the expansion and dysfunction of EAT. EAT is a facilitator of the pathophysiological process of HFpEF, which may promote inflammation, oxidative stress, myocardial steatosis, and myocardial fibrosis *via* vasocrine or paracrine mechanisms, ultimately contributing to LV remodeling and diastolic dysfunction. Accordingly, inhibition of the expansion of EAT may be an attractive therapeutic intervention for HFpEF with T2DM.

Currently, lifestyle management, bariatric surgery, and certain medications related to anti-cytokines, anti-hyperlipidemia, and anti-hyperglycemia can help to alleviate the inflammation and or accumulation of EAT and reduce clinical symptoms or improve long-term prognosis in patients with HFpEF. Nevertheless, the specific mechanisms by which these drugs inhibit EAT expansion remain to be further explored, and clinical studies on their use in HFpEF with T2DM are lacking. As a result, relevant foundational research and well-designed randomized controlled trials are needed to elucidate the pharmacological mechanisms and efficacy of current interventions. Another critical aspect is to develop new methods to suppress the inflammation or expansion of EAT. Concomitantly, it is essential to thoroughly investigate the mechanisms of abnormal accumulation of EAT so that more novel and effective therapies targeting EAT will become available.

CONCLUSION

In the development of HFpEF with T2DM, the expansion and dysfunction of EAT exert an essential role. Through vasocrine or paracrine pathways, abnormal EAT accumulation may lead to inflammation, oxidative stress, myocardial steatosis, and myocardial fibrosis, resulting in LV remodeling and diastolic dysfunction, which are essential features of HFpEF. Therefore, targeting EAT may be a prospective therapeutic intervention for HFpEF with T2DM. At present, lifestyle management, bariatric surgery, and pharmaceutical interventions may help alleviate the expansion of EAT and improve the clinical manifestations or prognoses of HFpEF patients. Nonetheless, well-designed randomized controlled studies are required to confirm the efficacy of existing treatments. Moreover, it is hoped that more novel and effective therapies targeting EAT will become available in the future.

FOOTNOTES

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