82803_Auto_EditedC.docx

WORD COUNT	3814	TIME SUBMITTED	13-APR-2023 02:19PM
		PAPER ID	98669476

Name of Journal: *World Journal of Diabetes*

Manuscript NO: 82803

Manuscript Type: REVIEW

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

Shi YJ *et al*. Adipose Tissue in HFpEF with Diabetes

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

Abstract

Heart failure (HF) 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 attenuates 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. Hopefully, more novel and effective therapies targeting EAT will become available 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

Shi Y, Dong G, Guo M. Targeting epicardial adipose tissue: A potential therapeutic strategy for heart failure with preserved ejection fraction with type 2 diabetes mellitus. *World J Diabetes* 2023; In press

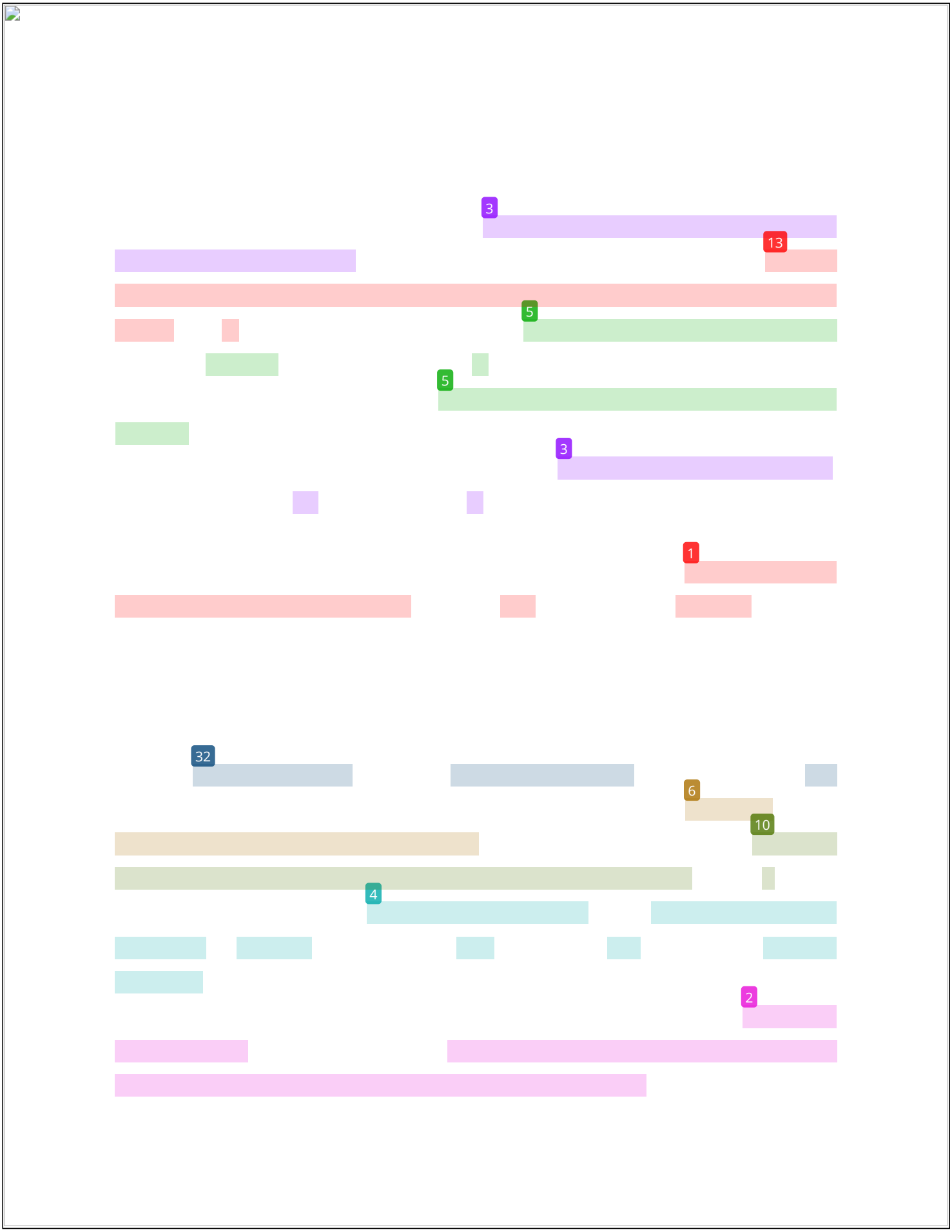
Core Tip: Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome. Effective interventions are lacking due to the complex pathophysiological underpinnings. Nevertheless, it is essential to provide individualized treatment depending on phenotypic differences. HFpEF with type 2 diabetes mellitus (T2DM) is a specific phenotype of HFpEF, and its emergence and progression are 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 T2DM. Currently, lifestyle management, bariatric surgery, and certain drugs related to anti-cytokines, anti-hyperglycemia, and anti-hyperlipidemia may help to suppress the accumulation of EAT and be beneficial in improving the clinical symptoms and prognosis of HFpEF patients. Accordingly, more standardized randomized controlled studies are required to validate the efficacy of current treatments. It is also essential to thoroughly understand the pathological mechanisms underlying the aberrant expansion of EAT, thus helping to develop new effective therapies.

INTRODUCTION

Heart failure (HF) 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 will evaluate the role of EAT in the development of HFpEF with T2DM and discuss current therapies to attenuate EAT expansion as well as future therapeutic perspectives.


3
13
5
5
3
1
32
6
10
4
2

energy as heat[16]. EAT might, therefore, provide direct heat to the myocardium and protect the heart under unfavourable 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 FFA under pathological conditions, triggering EAT expansion, localized hypoxia, and the infiltration of macrophages, ultimately resulting in a chronic inflammatory response[8]. Subsequently, numerous pro-inflammatory 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] have 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 FFA 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 pro-inflammatory adipocytokines and chemokines in EAT. These pro-inflammatory 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], an 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 confirmed that higher EAT was linked not only to LV hypertrophy and diastolic dysfunction but also to endothelial dysfunction[50]. 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[48,50-54]. 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, respectively.

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) for 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 six months 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 two weeks of continuous exercise 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 reduces 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-month 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.

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/day) reduced EAT thickness more significantly than simvastatin/ezetimibe (10/10 mg/day). Soucek *et al*[75] confirmed that substantial reductions in EAT were associated with intensive atorvastatin therapy (80 mg/day) in atrial fibrillation patients undergoing pulmonary vein isolation. A study by Alexopoulos *et al*[76] showed that intensive treatment (atorvastatin, 80 mg/day) was more successful in inducing EAT reduction than moderate-intensity treatment (pravastatin, 40 mg/day) 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 six months 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 three months 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 PPAR-γ[87]. As a result, it reduces the secretion of pro-inflammatory 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[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 patients with T2DM and overweight had a 15% reduction in EAT thickness after six months of treatment with a combination of metformin and sitagliptin, a DPP-4 inhibitor. Unfortunately, there is a lack of research on regulating EAT using DPP4 alone. Therefore, relevant studies still need to support whether DPP-4 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) is 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 Díaz-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 pro-inflammatory chemokines *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 prognosis 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.

82803_Auto_EditedC.docx

ORIGINALITY REPORT

18%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.researchgate.net Internet	119 words — 3%
2	www.ncbi.nlm.nih.gov Internet	92 words — 2%
3	"Epicardial Adipose Tissue", Springer Science and Business Media LLC, 2020 Crossref	46 words — 1%
4	Elisa Doukbi, Astrid Soghomonian, Coralie Sengenès, Shaista Ahmed, Patricia Ancel, Anne Dutour, Bénédicte Gaborit. "Browning Epicardial Adipose Tissue: Friend or Foe?", Cells, 2022 Crossref	33 words — 1%
5	studyres.com Internet	30 words — 1%
6	Mi-Na Kim, Hack-Lyoung Kim, Seong-Mi Park, Mi Seung Shin, Cheol Woong Yu, Myung-A Kim, Kyung-Soon Hong, Wan-Joo Shim. "Association of epicardial adipose tissue with coronary spasm and coronary atherosclerosis in patients with chest pain: analysis of data collated by the KoRean wOmen'S chest pain rEgistry (koROSE)", Heart and Vessels, 2017 Crossref	28 words — 1%

7	worldwidescience.org Internet	28 words — 1%
8	www.mdpi.com Internet	25 words — 1%
9	Milton Packer. "Drugs That Ameliorate Epicardial Adipose Tissue Inflammation May Have Discordant Effects in Heart Failure With a Preserved Ejection Fraction as Compared With a Reduced Ejection Fraction", Journal of Cardiac Failure, 2019 Crossref	23 words — 1%
10	Gianluca Iacobellis, Antonio C. Bianco. "Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features", Trends in Endocrinology & Metabolism, 2011 Crossref	21 words — 1%
11	www.science.gov Internet	21 words — 1%
12	biointerfaceresearch.com Internet	19 words — < 1%
13	scholars.lib.ntu.edu.tw Internet	17 words — < 1%
14	Bharathi Upadhya, Dalane W. Kitzman. "Management of Heart Failure with Preserved Ejection Fraction: Current Challenges and Future Directions", American Journal of Cardiovascular Drugs, 2017 Crossref	14 words — < 1%
15	Grigorios Korosoglou, Per M. Humpert, Johannes Ahrens, Dimitrios Oikonomou et al. "Left ventricular diastolic function in type 2 diabetes mellitus is	13 words — < 1%

associated with myocardial triglyceride content but not with impaired myocardial perfusion reserve", Journal of Magnetic Resonance Imaging, 2012
Crossref

16 Handbook of Anthropometry, 2012.
Crossref
13 words — < 1%

17 Kenji Harada. "DOPPLER ECHOCARDIOGRAPHIC DETECTION OF ABNORMAL DIASTOLIC FILLING IN FETUSES WITH DUCTAL CONSTRICTION. ??? 158", Pediatric Research, 04/1996
Crossref
13 words — < 1%

18 Van Tassell, Benjamin Wallace, Ross Arena, Giuseppe Biondi-Zoccai, Justin McNair Canada, Claudia Oddi, Nayef Antar Abouzaki, Arehzo Jahangiri, Raquel Appa Falcao, Michael Christopher Kontos, Keyur Bharat Shah, Norbert Felix Voelkel, Charles Anthony Dinarello, and Antonio Abbate. "Effects of Interleukin-1 Blockade with Anakinra on Aerobic Exercise Capacity in Patients with Heart Failure and Preserved Ejection Fraction (from the D-HART Pilot Study)", The American Journal of Cardiology, 2013.
Crossref
13 words — < 1%

19 www.hindawi.com
Internet
12 words — < 1%

20 Niklas Pakkasjärvi, Veera Hölttä, Jukka Heikkilä, Seppo Taskinen. "Posterior urethral valves and the risk of neurodevelopmental disorders in two FINNISH cohorts", Journal of Pediatric Urology, 2021
Crossref
11 words — < 1%

21 www.degasperis.it
Internet
11 words — < 1%

22	Angela Ceribelli, Francesca Motta, Maria De Santis, Aftab A. Ansari, William M. Ridgway, M. Eric Gershwin, Carlo Selmi. "Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy", Journal of Autoimmunity, 2020 Crossref	10 words — < 1%
23	Gianluca Iacobellis. "Epicardial adipose tissue in endocrine and metabolic diseases", Endocrine, 2013 Crossref	10 words — < 1%
24	archive.org Internet	10 words — < 1%
25	www.sciencegate.app Internet	10 words — < 1%
26	www.scilit.net Internet	10 words — < 1%
27	www.semanticscholar.org Internet	10 words — < 1%
28	journals.plos.org Internet	9 words — < 1%
29	www.e-dmj.org Internet	9 words — < 1%
30	www.unboundmedicine.com Internet	9 words — < 1%
31	"Tuesday, 6 September 2005", European Heart Journal, 09/02/2005 Crossref	8 words — < 1%

32	pure.rug.nl Internet	8 words — < 1%
33	www.cpdexpress.co.za Internet	8 words — < 1%
34	www.publicatie-online.nl Internet	8 words — < 1%
35	www.wjgnet.com Internet	8 words — < 1%
36	"Sunday, 31 August 2008", European Heart Journal, 09/02/2008 Crossref	7 words — < 1%
37	Pavan Bhat, W.H. Wilson Tang. "Future Therapies in HFpEF", Elsevier BV, 2021 Crossref	6 words — < 1%
38	Sophie Van Linthout, Carsten Tschöpe. "The Quest for Antiinflammatory and Immunomodulatory Strategies in Heart Failure", Clinical Pharmacology & Therapeutics, 2019 Crossref	6 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF