Received: 14 October 2025 | Revised: 11 November 2025 | Accepted: 17 November 2025

DOI: 10.1111/dom.70324

REVIEW ARTICLE

WILEY

Heart matters: How glucose- and lipid-modulating drugs remodel epicardial adipose tissue accumulation, inflammatory patterns and browning

Elisabeth Heuboeck MSc[1,2] | Charnkamal Singh Bhogal BSc[1,2] | Markus Mandl PhD[1,2]

[1]Department of Pathophysiology, Institute for Physiology and Pathophysiology, Johannes Kepler University Linz, Linz, Austria

[2]Medical Faculty, Clinical Research Institute for Cardiovascular and Metabolic Diseases, Johannes Kepler University Linz, Linz, Austria

Correspondence
Elisabeth Heuboeck, Department of Pathophysiology, Institute for Physiology and Pathophysiology, Johannes Kepler University Linz, Krankenhausstrasse 5, 4020 Linz, Austria.
Email: elisabeth.heuboeck@jku.at

Funding information
Open Access Publication Fund of the Johannes Kepler University Linz and the federal state Upper Austria

Abstract

Epicardial adipose tissue (EAT) is a metabolically active visceral fat depot located between the myocardium and the visceral pericardium, exerting direct paracrine and vasocrine effects on the heart and coronary vessels. Under physiological conditions, EAT supports myocardial energy metabolism and thermoregulation through fatty acid supply and adaptive metabolic flexibility. In cardiometabolic disorders such as obesity, type 2 diabetes, and heart failure, EAT undergoes pathological remodelling characterized by increased thickness, adipocyte hypertrophy, immune cell infiltration, and secretion of pro-inflammatory and fibrotic mediators. These alterations contribute to myocardial fibrosis, stiffness, and coronary atherosclerosis, particularly in heart failure with preserved ejection fraction. Pharmacological modulation of EAT has therefore emerged as a promising therapeutic approach in cardiovascular prevention. Agents such as statins, peroxisome proliferator-activated receptor gamma agonists, adenosine monophosphate–activated protein kinase activators, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors exert both systemic and depot-specific effects. They reduce EAT thickness, suppress inflammatory signalling, enhance insulin sensitivity, and promote adipocyte browning and oxidative metabolism. Among these, sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists show the most consistent effects in shifting EAT towards a less inflammatory and more metabolically active phenotype. The goal of this review is to provide an overview of current pharmacological interventions that influence EAT and to summarize how much is known about their molecular mechanisms from in vitro and in vivo studies. The target audience includes cardiovascular researchers and clinicians seeking to better understand how metabolic and antidiabetic therapies modulate cardiac fat biology and function.

KEYWORDS

adipocyte browning, AMPK activators, cardiometabolic remodelling, epicardial adipose tissue, GLP1R-agonists, heart failure, inflammation, obesity, PPARγ activators, SGLT2i, statins

1 | INTRODUCTION

Epicardial adipose tissue (EAT) is a distinct visceral fat depot located between the myocardium and the visceral layer of the pericardium.[1] Unlike other fat stores, EAT is uniquely positioned to interact directly with the heart and coronary vessels, secreting a variety of adipokines, cytokines, and bioactive factors that influence cardiac metabolism, vascular function, and electrophysiological properties.[2] Figure 1 shows the distinct physiological proximity of these two tissues, where EAT can be observed adjacent directly to the right ventricle when the pericardial sac is opened during cardiac bypass graft. Under normal physiological conditions, EAT contributes to myocardial energy homeostasis by serving as a readily accessible source of free fatty acids. It exhibits metabolic flexibility, and provides thermogenic protection during periods of increased cardiac workload.[3]

In cardiometabolic diseases such as obesity, type 2 diabetes mellitus (T2DM), and heart failure, EAT undergoes significant expansion and functional changes.[4] Importantly, EAT dysfunction often arises early in the course of metabolic syndrome, preceding overt obesity or diabetes. This early remodelling—marked by adipocyte hypertrophy and hyperplasia, immune cell infiltration, and a pro-inflammatory, pro-fibrotic, and insulin-resistant secretory profile—creates a metabolically active and inflammatory microenvironment.[4] These alterations can impair myocardial relaxation, promote coronary atherosclerosis, and contribute to myocardial fibrosis and stiffening, thereby facilitating the development of heart failure with preserved ejection fraction (HFpEF), coronary artery disease (CAD), and other major adverse cardiovascular events.[5–8] Given the critical role of EAT in linking metabolic dysfunction with cardiovascular disease, it has emerged as an attractive target for therapeutic intervention. Several glucose- and lipid-modulating drugs—including statins, Peroxisome-Proliferator-Activator-Receptor-γ (PPARγ) agonists, adenosine monophosphate–activated protein kinase (AMPK) activators, glucagon-like-peptide-1 (GLP1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors—have been shown to impact EAT by reducing its volume, attenuating inflammation, improving insulin sensitivity, and enhancing myocardial energetics through diverse molecular mechanisms.[9–12]

This review focuses on the current understanding of how these pharmacologic agents influence EAT biology. After outlining the development and physiological functions of EAT, we discuss its pathological remodelling in cardiometabolic disease. We then examine the evidence supporting the modulation of EAT by glucose- and lipid-targeting therapies, highlighting both mechanistic insights and potential clinical implications for cardiovascular risk reduction.

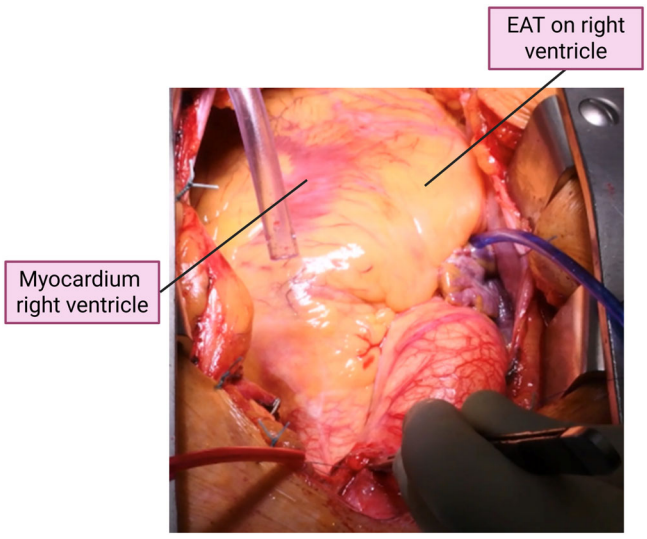

FIGURE 1 Epicardial adipose tissue is located directly on top of the myocardial surface of the right ventricle, picture obtained during sternotomy. Created in BioRender. Reingruber, S. (2025) https://BioRender.com/vfymzc3.

2 | PHYSIOLOGICAL PROPERTIES—EAT AS ENERGY STORAGE AND THERMOGENIC PROTECTOR OF THE MYOCARDIUM

Metabolically, EAT is regarded as the visceral fat depot of the heart. While primarily composed of white, unilocular adipose tissue, small depots of brown, multilocular adipocyte niches have been identified in perivascular regions—such as the aorta and common carotid artery—and near the epicardial surface.[13] During fetal and early neonatal life, EAT exhibits several morphological and molecular features characteristic of brown adipose tissue (BAT).[14] These include, as mentioned, the presence of multilocular lipid droplets, dense mitochondrial content, and expression of thermogenic markers such as uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), and PR domain containing 16 (PRDM16).[15–17] This thermogenic profile is hypothesized to protect the immature myocardium from thermal stress and to provide a local energy reservoir for rapidly metabolizing cardiac tissue. Unlike classical brown fat depots however, EAT is presumed not to originate from Myf5+ precursors, but from the splanchnopleuric mesenchyme,[18] and also expresses CD137, a marker characteristic of beige adipose tissue.[19] This supports its classification as a beige or inducible brown fat, capable of transitioning between 'brown' and 'white' adipose tissue during aging.[14,19,20] In its healthy, non-pathological state, EAT performs a number of important physiological roles. It serves as a local buffer for free fatty acids, supplying high-energy substrates directly to the myocardium through shared coronary microcirculation.[3,21,22] This unique vascular relationship also enables rapid paracrine and vasocrine signalling between EAT and the underlying cardiac tissue. In addition, EAT produces cardioprotective adipokines, including adiponectin and omentin, which exert anti-inflammatory, anti-fibrotic, and vasodilatory effects.[23–27] The anatomical distribution of EAT, particularly along the coronary arteries, also provides mechanical protection and insulation to the myocardium.[28] Although much of the early thermogenic phenotype is lost in adulthood[19] the metabolic flexibility and endocrine function of EAT suggest it retains a key role in cardiac energy homeostasis and protection under physiological conditions.[29] Beyond serving as an energy buffer,

brown and beige adipocytes within EAT actively contribute to myocardial energy homeostasis through metabolic and thermogenic coupling.[8,28] Their dense mitochondrial content enables high rates of β-oxidation and uncoupled respiration, generating both ATP and heat to support the heart's high and fluctuating energy demands.[30–32] Free fatty acids released from thermogenic adipocytes can be rapidly utilized by adjacent cardiomyocytes via the shared coronary microcirculation, while localized heat production may enhance enzymatic efficiency and protect against ischemic stress.[7,33–35] This 'energetic crosstalk' positions EAT not merely as an insulating or endocrine organ, but as an active metabolic partner of the myocardium—one that adjusts substrate supply and thermogenesis in response to cardiac workload and systemic metabolic cues. With advancing age and increasing cardiometabolic burden, EAT undergoes a phenotypic shift towards a white adipose tissue (WAT)-like profile. This transition is marked by a progressive loss of UCP1 expression and other thermogenic gene signatures, a shift from multilocular to unilocular adipocyte morphology, and decreased mitochondrial density.[3,19] While this shift may be part of normal maturation, it is accelerated in the context of obesity, diabetes, and CAD.[36–39] These pathological states induce local hypoxia, oxidative stress, and infiltration of immune cells, further repressing thermogenic programs and promoting fibrotic and inflammatory remodelling of the tissue.[3] Interestingly, this loss of browning capacity in EAT does not necessarily correlate with reductions in its volume. Indeed, increased EAT volume has been consistently observed in individuals with metabolic syndrome, T2DM, and heart failure, particularly HFpEF.[3] Rather than serving a thermogenic or energy-buffering function, EAT in these contexts becomes a source of pro-inflammatory adipokines (e.g., Interleukin-6 (IL-6), tumour-necrosis-factor-α (TNF-α), resistin) and fibrotic mediators, contributing to myocardial stiffness, arrhythmogenesis, and atherosclerosis.[40–42] The phenotypic shift from brown-like to white adipose tissue with age and metabolic stress marks a critical turning point—where EAT transitions from being a cardioprotective depot to a potential contributor to cardiovascular pathology.

3 | CLINICAL ASSESSMENT OF EAT

Accurate assessment of EAT is essential for both research and clinical interpretation. The main non-invasive imaging modalities include echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI). While echocardiography is widely accessible, inexpensive, and allows rapid estimation of EAT thickness, it is limited to linear measurements at select locations and highly operator-dependent,[43] whereas CT and MRI are considered the non-invasive gold standards for clinical studies on EAT, including pharmacologic interventions discussed in this review. CT provides high-resolution three-dimensional measurement of EAT volume and permits tissue characterization via EAT attenuation values.[44,45] These are frequently observed in imaging studies on HFpEF and CAD. Attenuation provides a marker for fat density and inflammation of the tissue. Lower (more negative) attenuation values indicate lipid-rich, less inflamed adipose tissue, whereas higher attenuation values reflect reduced lipid content, fibrosis, and inflammatory infiltration.[46] CT's main limitations are exposure to ionizing radiation and the need for contrast in some protocols.[47] MRI also offers excellent soft-tissue contrast, allowing accurate volumetric and functional assessment in 3D without radiation.[48,49] It is ideal for longitudinal studies but is less widely available and more time-consuming than CT.

4 | EAT IN HEART FAILURE AND CARDIOMETABOLIC DISEASES

In the context of metabolic diseases such as obesity, T2DM and heart failure, EAT undergoes remodelling characterized by volumetric expansion and a shift in its secretory profile towards a pro-inflammatory, pro-fibrotic, and insulin-resistant phenotype.[5,50] EAT pathological conditions are characterized by an altered secretome, where protective adipokines such as adiponectin are downregulated, while pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and resistin are overexpressed.[51,52] These cytokines contribute not only to local myocardial inflammation but also to systemic inflammation and insulin resistance, thereby linking EAT dysfunction with the broader metabolic derangements, characteristic of obesity and diabetes.[7] TNF-α, a central mediator of inflammation, promotes endothelial dysfunction and apoptosis of cardiomyocytes, exacerbating myocardial injury and fibrosis.[53,54] Resistin, initially described for its role in insulin resistance, has been implicated in promoting vascular inflammation and atherogenesis and is highly expressed in epicardial adipose tissue of patients suffering from heart failure and CAD.[55,56] Together, these factors contribute to a pro-fibrotic environment resulting in myocardial stiffening and impaired diastolic relaxation.[4] Due to the physical proximity of the tissues, pathological transformation of EAT significantly contributes to cardiac remodelling, increased left ventricular mass,[57] myocardial fibrosis, impaired diastolic function,[34,58] accelerated coronary atherosclerosis and electromechanical changes due to pro-inflammatory signalling.[50,59] The increased EAT volume observed in these cardiometabolic conditions reflects hypertrophy and hyperplasia of adipocytes within the fat, as well as infiltration by immune cells such as macrophages, which intensify the local inflammation.[7,60] In parallel with this inflammatory shift, the loss of brown and beige adipocyte features within EAT due to hypertrophy of white adipocytes reduces mitochondrial oxidative capacity and β-oxidation, diminishing its ability to supply the myocardium with readily available fatty acids and thermogenic energy support.[3,7,31,33] The resulting decline in this local energy-buffering function may exacerbate myocardial metabolic stress, further contributing to impaired relaxation and contractile inefficiency, particularly in the early stages of HFpEF.[22,31,61] Clinically, this pathological remodelling of EAT is most evident in HFpEF, a syndrome characterized by diastolic dysfunction and increased myocardial stiffness.[62,63] Multiple studies have demonstrated that patients with HFpEF exhibit significantly increased EAT volumes compared to controls, with strong

correlations between EAT burden and markers of left ventricular (LV) stiffness as well as exercise intolerance.[62] Mechanistically, the pro-inflammatory adipokine milieu of EAT in HFpEF appears to drive myocardial fibrosis and microvascular endothelial dysfunction, both key pathophysiological features of this syndrome.[64] Moreover, EAT's anatomical proximity to the coronary arteries and myocardium allows its secreted bioactive molecules to exert paracrine effects that directly influence coronary atherosclerosis. EAT-derived inflammatory cytokines promote endothelial activation, smooth muscle proliferation, and recruitment of immune cells within the vascular wall, accelerating plaque formation and instability.[3,5] This link between EAT inflammation and coronary artery disease (CAD) has been substantiated by imaging studies showing that increased EAT volume predicts coronary plaque formation and adverse cardiovascular events independently of traditional risk factors (e.g., BMI or lipoprotein levels).[65] Conditions like metabolic syndrome, insulin resistance, and chronic low-grade inflammation promote the expansion, attenuation and therefore dysfunction of EAT.[7,32] In turn, this dysfunctional fat depot releases harmful signals that contribute to adverse changes in the heart muscle and blood vessels.[7] This cycle of EAT metabolism and cardiac function negatively influencing each other reinforces itself over time, worsening both metabolic and cardiovascular health. Recognizing this dynamic, EAT has emerged not just as a marker of disease, but as a promising target for therapy. Therapeutic strategies that also reduce EAT volume or shift its secretory profile towards a more anti-inflammatory, cardioprotective state—such as SGLT2 inhibitors, statins, GLP-1 receptor agonists, and PPARγ agonists—are currently attracting significant interest among researchers exploring EAT's role in cardiometabolic disease and obesity. These agents hold promise not only for improving metabolic control but also for mitigating cardiovascular risk by directly modulating EAT. Restoring the thermogenic and energy-supporting phenotype of EAT—through reactivation of browning pathways and enhanced mitochondrial function—offers a mechanistic route to re-establish both metabolic and inflammatory balance at the heart–fat interface. In this review, we take a closer look at the current evidence on how these drug classes affect EAT biology and what this could mean for future therapeutic approaches.

5 | IMPACT OF GLUCOSE- AND LIPID-MODULATING DRUGS ON EPICARDIAL ADIPOSE TISSUE

Beyond their systemic metabolic effects, several orally administered glucose- and lipid-modulating agents exert direct effects on EAT, influencing its volume, cellular phenotype, and secretory, pro- and anti-inflammatory signalling profile. These effects appear to be beyond weight reduction or glycemic control, implicating mechanisms such as improved adipocyte mitochondrial function, reduced oxidative stress, modulation of local immune cell populations, and attenuation of pro-inflammatory signalling pathways.[10,22,66] Increasing evidence suggests that pharmacologically targeting EAT may contribute to the cardiovascular benefits observed with drugs commonly used in patients with cardiometabolic disease. The hypothesized modes of action of these compounds are summarized in Figure 2 and Table 1. In the following sections, we explore the current knowledge regarding the impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor (GLP-1R) agonists, statins, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, and AMP-activated protein kinase (AMPK) activators on EAT, with a focus on their mechanistic effects and potential therapeutic implications.

5.1 | Statins

Beyond their established LDL-cholesterol–lowering effects, statins exert pleiotropic anti-inflammatory and metabolic actions that extend into perivascular adipose tissue.[67] Here, we review drug-specific evidence on statins and EAT, followed by mechanistic insights into potential pathways of action.

5.1.1 | Atorvastatin

Atorvastatin is the most extensively investigated statin with respect to EAT. In the Ossabaw swine model of metabolic syndrome, long-term atorvastatin treatment significantly remodelled the epicardial adipose tissue transcriptome, with enrichment of interferon-α/γ signalling pathways and concomitant downregulation of pro-inflammatory networks involving TNF-α signalling, IL-6–Janus Kinase (JAK), Signal Transducer and Activator of Transcription 3 (STAT3), and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)–related genes, highlighting a shift in EAT towards a less inflammatory and more immunoregulatory phenotype.[68] In clinical studies, high-intensity atorvastatin has consistently demonstrated reductions in EAT volume and attenuation.[67,69] For example, in a substudy of the BELLES trial, hyperlipidemic postmenopausal women were randomized to receive either atorvastatin 80 mg/day or pravastatin 40 mg/day for 1 year.[71] The results demonstrated that atorvastatin treatment led to a significant reduction in EAT volume compared to pravastatin. Importantly, this reduction in EAT volume was not correlated with changes in lipid levels, suggesting that the effect was independent of LDL-C lowering and may be attributed to other pleiotropic actions of statins, such as anti-inflammatory effects.[71] Patients with atrial fibrillation undergoing ablation can also benefit from statin therapy, as 3 months of high-dose atorvastatin (80 mg/day) have been shown to significantly reduce epicardial adipose tissue (EAT) volume and attenuation, as measured by cardiac CT, effects that were also independent of changes in LDL-C, suggesting direct action on EAT.[69] This finding was reinforced by Raggi et al., who showed that both atorvastatin and pravastatin reduced epicardial adipose tissue (EAT) attenuation, a CT-based marker of inflammation, with the effect being more pronounced for atorvastatin—again independently of LDL-C reduction.[67] Collectively, atorvastatin exerts reproducible effects on EAT,

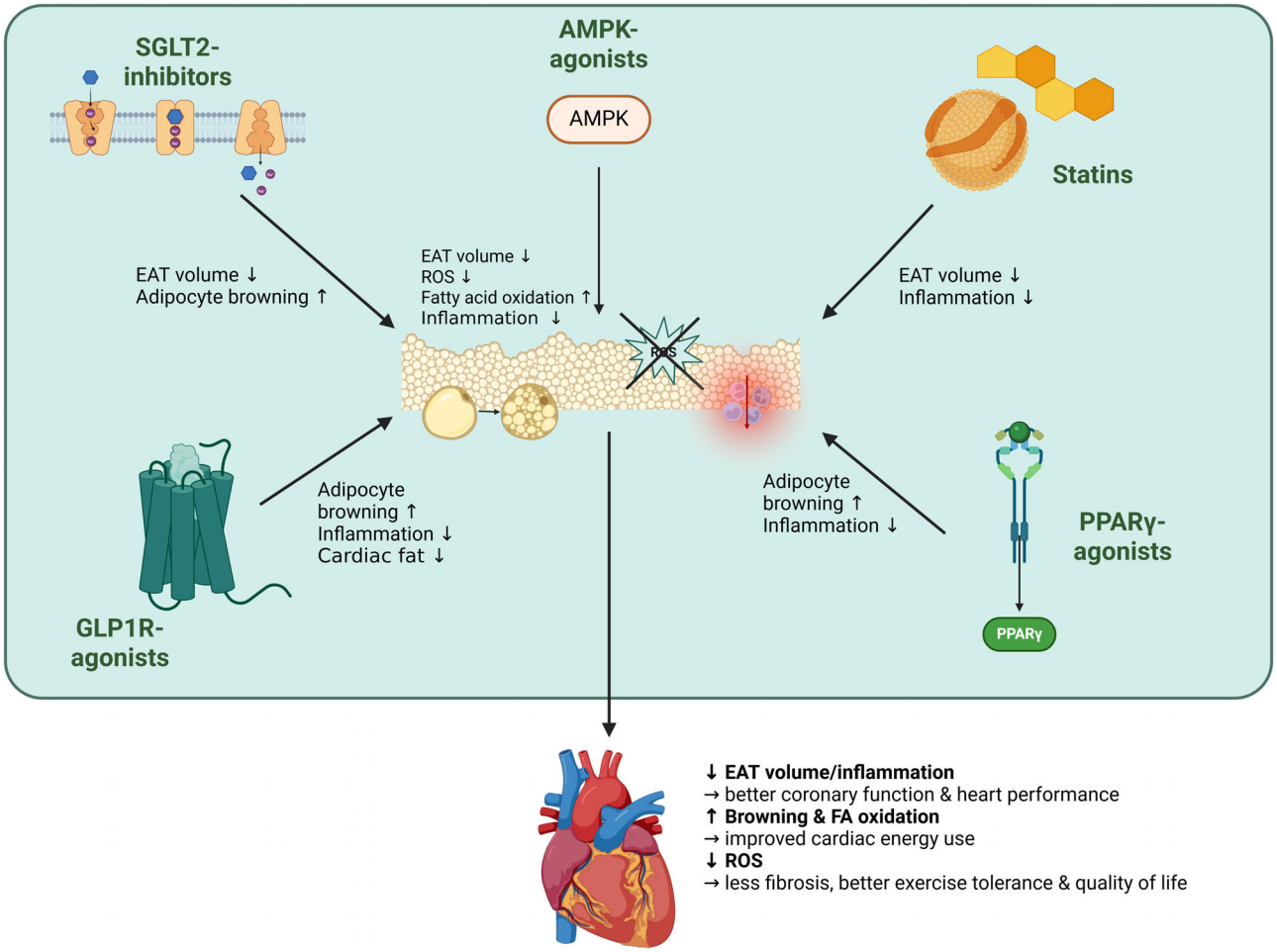

FIGURE 2 Generalized effects of statins, PPARγ agonists, AMPK agonists, SGLT2i and GLP1R agonists on EAT, which in turn modulate cardiac function and patient quality of life. SGLT2 inhibitors primarily act by reducing overall EAT volume and promoting adipocyte browning, thereby shifting the tissue towards a more metabolically favourable state. AMPK agonists decrease EAT mass and reactive oxygen species while enhancing fatty acid oxidation, collectively attenuating tissue inflammation. Statins exert their effects mainly through cholesterol lowering, leading to reductions in EAT volume and inflammatory activity—similar to PPARγ agonists, which additionally stimulate adipocyte browning. GLP-1 receptor agonists likewise promote browning and reduce overall cardiac fat content alongside inflammatory signalling. Created in BioRender. Reingruber, S. (2025) https://BioRender.com/3mkowl4.

both quantitatively (volume regression) and qualitatively (reduced inflammatory activity). These effects occurred independently of systemic lipid lowering, resulting in lowered risk of atrial fibrillation, heart failure due to EAT mechanically obstructing the heart and less fibrotic remodelling due to inflammatory signalling.

5.1.2 | Rosuvastatin

Data on rosuvastatin is comparatively sparse. Jo et al.[72] investigated the effects of aerobic exercise in combination with Rosuvastatin/Olmesartan therapy in patients with hypertension and dyslipidemia and found a significant reduction of epicardial fat thickness, though the single effect of rosuvastatin cannot exactly be determined, especially since olmesartan alone has also been shown to reduce EAT in clinical studies.[73]

5.1.3 | Simvastatin

In patients with metabolic syndrome undergoing coronary bypass surgery, 3 months of simvastatin (20 mg) reduced inflammatory gene expression (including *IL-6*, *leptin*, *resistin*, and *monocyte chemoattractant protein-1* (*MCP-1*)) in EAT excised during surgery as well as in plasma.[74] In combination with pioglitazone (a PPARγ agonist), simvastatin produced additive anti-inflammatory results.[74] In a retrospective cohort of patients undergoing PCI, simvastatin (10 mg) combined with ezetimibe (10 mg) significantly reduced echocardiographic epicardial fat thickness, mirroring the lipid-lowering effects seen with atorvastatin, though later comparisons demonstrated that atorvastatin alone produced a larger reduction in EAT thickness.[11] These findings suggest that simvastatin does alter EAT biology, particularly with respect to inflammation; however effects seem to be less potent than atorvastatin.

TABLE 1 Effects of pharmacologic agents on epicardial adipose tissue (EAT).

Drug class	Key drugs	Effects on EAT	Proposed mechanisms	Strength of evidence	References
Statins	Atorvastatin	↓ EAT volume, ↓ attenuation, ↓ inflammation, possible browning	NF-κB inhibition, M1 → M2 macrophage shift, ↑ mitochondrial FAO, thermogenic gene induction	Preclinical + Clinical	[11,48,66–70]
	Rosuvastatin	↓ EAT thickness (confounded by combination therapy)	Unclear; likely pleiotropic anti-inflammatory effects	Limited Clinical	[71,72]
	Simvastatin	↓ inflammatory gene expression, modest ↓ EAT thickness	NF-κB inhibition, anti-inflammatory	Preclinical + Clinical	[73,74]
	Pravastatin	Modest ↓ EAT volume and attenuation	Anti-inflammatory, less potent than atorvastatin	Clinical	[67,69]
PPARγ agonists	Pioglitazone	↓ EAT volume, ↓ pro-inflammatory cytokines	↑ adiponectin, M1 → M2 macrophage shift, mitochondrial biogenesis, partial browning	Preclinical + Clinical	[75–79]
	Rosiglitazone	Browning, M1 → M2 macrophage shift	↑ PRDM16, ↑ UCP1, mitochondrial biogenesis	Preclinical	[79,80]
AMPK activators	Metformin	↓ EAT thickness, ↓ inflammation	↑ fatty acid oxidation, ↓ lipogenesis, NF-κB inhibition, ↑ adiponectin, M1 → M2 shift	Clinical + Preclinical	[81–87]
GLP-1R agonists	Liraglutide	↓ EAT volume and thickness, ↑ thermogenic genes, ↓ inflammatory cytokines	Direct GLP-1R activation, AMPK–PGC-1α signalling, ↑ UCP1/mitochondrial biogenesis, M2 macrophage shift	Preclinical + Clinical	[10,88–95]
	Semaglutide	↓ EAT thickness/volume, ↓ inflammatory/adipogenic signalling, ↑ mitochondrial proteins	Browning, oxidative metabolism enhancement, paracrine anti-inflammatory effects	Preclinical + Clinical	[10,96–101]
	Exenatide	↓ EAT volume/thickness, ↑ oxidative markers	Browning, ↑ lipolysis/oxidation, ↓ adipogenic gene expression	Preclinical + Clinical	[102–104]
	Tirzepatide	↓ paracardiac adipose tissue (likely includes EAT)	GLP-1/GIP mediated weight loss and anti-inflammatory effects	Clinical (indirect)	[105–107]
SGLT2 inhibitors	Dapagliflozin	↓ EAT volume, ↓ lactate release, ↑ browning markers	↑ mitochondrial oxidation, ↑ UCP1/PRDM16, ↓ IL-6/MCP-1, M1 → M2 shift	Preclinical + Clinical	[108–116]
	Empagliflozin	↓ EAT volume (select populations), ↓ pro-inflammatory cytokines	↑ FA oxidation, browning, M1 → M2 macrophage shift	Preclinical + Clinical	[117–121]
	Canagliflozin/ Luseogliflozin/ Ipragliflozin	↓ EAT volume, ↓ systemic inflammation	Likely similar mechanisms to dapagliflozin/ empagliflozin	Limited Clinical	[122–125]

Note: Summary of key drug classes and individual agents affecting EAT. For each, observed effects on volume, thickness, attenuation, inflammation, and browning are listed, along with primary mechanisms, strength of evidence (preclinical or clinical), and supporting references. This overview allows direct comparison of therapeutic impacts on EAT and their potential cardiovascular implications.

5.1.4 | Pravastatin

Pravastatin has mainly served as a comparator: In the BELLES sub-study, pravastatin 40 mg was associated with modest reductions in EAT volume, significantly smaller than those with atorvastatin 80 mg.[67,71] In a trial of postmenopausal women, pravastatin reduced EAT attenuation over 1 year, consistent with decreased inflammatory activity, though the effect again was weaker than atorvastatin.[67]

5.1.5 | Lovastatin, fluvastatin and pitavastatin

No direct experimental or clinical evidence is currently available for lovastatin, fluvastatin, or pitavastatin in relation to EAT. Reviews of statin therapy as a class conclude that EAT regression is a consistent finding with intensive statin therapy, but whether these lesser-studied agents replicate the magnitude of effect seen with atorvastatin remains uncertain.[3,126,127]

5.1.6 | Mechanistic pathways of statins

Statins appear to modulate EAT through a constellation of pleiotropic mechanisms that extend well beyond LDL-cholesterol lowering. By inhibiting the mevalonate pathway, statins reduce the availability of isoprenoids required for the prenylation of small monomeric guanidinium-triphosphatases (GTPases) such as Rho, Rac, and Ras, thereby suppressing NF-κB–mediated transcription of pro-inflammatory cytokines including *IL-6*, *TNF-α*, and *MCP-1*.[128,129] This effect is supported by human biopsy data demonstrating decreased

expression of inflammatory genes in EAT and plasma samples following simvastatin therapy[74] and by imaging studies showing reduced EAT attenuation on CT, consistent with lower tissue adipose immune activation.[67] In parallel, transcriptomic analyses suggest that statins enhance mitochondrial fatty acid oxidation while downregulating lipid synthesis, a metabolic reprogramming that likely contributes to volumetric regression and the formation of less and smaller adipocytes.[130,131] Immune remodelling appears central when looking at pro-inflammatory and anti-inflammatory cytokine signalling, as statins can shift macrophage polarization away from a pro-inflammatory M1 phenotype towards an anti-inflammatory M2 profile, thereby reducing IL-1β and TNF-α secretion while enhancing IL-10 and TGF-β production.[70,132] Statins have also been hypothesized to enhance the browning of EAT, characterized by increased expression of thermogenic genes such as *UCP1*, indicative of a transition from a white to a beige adipocyte phenotype. This browning effect is thought to further enhance the metabolic activity and thermogenic capacity of EAT, potentially offering additional cardioprotective benefits.[3] However, literature on the browning effects of statins remains scarce and somewhat contradictory, as other studies suggest that statins may inhibit adipose tissue browning.[75,133,134] Because of its anatomic continuity with the coronary adventitia, EAT-derived mediators directly influence the coronary vasculature and myocardium; thus, statin-induced reductions in pro-inflammatory cytokines and leptin, together with increases in adiponectin, may stabilize atherosclerotic plaques and reduce arrhythmogenic substrates.[4]

5.2 | PPARγ agonists

PPARγ agonists (e.g., pioglitazone) promote adipocyte differentiation and enhance insulin sensitivity.[76–78] In EAT, they may shift the adipokine profile towards a more anti-inflammatory state, increasing adiponectin while reducing TNF-α and IL-6. Despite concerns about fluid retention, their modulatory effects on EAT may partly explain their benefit in selected patients with diabetes and cardiovascular risk as described in detail below.

5.2.1 | Pioglitazone

Both pro- and anti-inflammatory cytokines, such as IL-1Ra and IL-1β, are upregulated in EAT of CAD patients who additionally present with either metabolic syndrome or type 2 diabetes. In a study of seven type 2 diabetes patients, pioglitazone treatment with a dose of 25 mg/day for a duration of 24 months initiated a decreased expression of IL-1Ra, IL-10 and IL-1β, thus reducing the expression of various pathologically elevated pro-inflammatory cytokines.[79] Further, pioglitazone has also been demonstrated to reduce the concentration of pro-inflammatory substances in the subcutaneous and visceral fat depots.[80] Macrophage-derived factors are known to stimulate the expression of pro-inflammatory adipokines such as *IL-6* and *IL-8* in adipose tissue and isolated adipocytes.[135] Ex-vivo tissue treated with pioglitazone prior to conditioned macrophage medium exposure showed a reduced expression of several pro-inflammatory substances including *IL-6*.[80] Moreover, it also reduced the adipokine lowering effect of macrophage factors as macrophages that had been exposed to pioglitazone triggered a weaker inflammatory response in control adipocytes, confirmed by a reduced TNF-α concentration.[80] The effect of pioglitazone on EAT was also evident in a clinical study consisting of 12 type 2 diabetes patients treated over a period of 24 weeks. The dose was increased gradually (5–45 mg/day over 24 weeks). MRI scans were conducted subsequently and revealed overall larger EAT areas in type 2 diabetes patients; however, EAT volume decreased significantly by 9% after the treatment. Also, left ventricular diastolic function as well as insulin sensitivity were found to be inversely correlated with EAT volume, as both improved after treatment.[77] Collectively these studies suggest that pioglitazone reduces pro-inflammatory processes in EAT as well as its overall volume, thereby culminating in a significant clinical improvement of cardiometabolic function including insulin sensitivity in EAT.

5.2.2 | Rosiglitazone

Relatively few studies have investigated rosiglitazone's effects on EAT, largely due to historical cardiovascular safety concerns, limited contemporary use and research focus shifting towards newer cardiometabolic drugs, as analysed in this review. However, a short-term study on the effects of rosiglitazone in an in vivo rat model system for diabetes has shown that rosiglitazone can induce the *PRDM16* as well as *UCP-1*. This leads to browning of EAT, which is advantageous for cardiometabolic health as the increased lipid turnover of BAT limits the release of fatty acids by EAT which would otherwise accumulate in the myocardium.[136] Moreover, rosiglitazone in vivo can shift macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 state.[78]

5.2.3 | Mechanistic pathways of PPARγ agonists

PPARγ agonists increase the expression of *PRDM16*, *Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α)* and *UCP-1*. This can lead to a change in the white phenotype of adipose tissue towards brown/beige adipose tissue, thereby promoting mitochondrial biogenesis. This was confirmed by high expression levels of *NADH dehydrogenase subunit 1 (ND1)* and *Cytochrome C oxidase subunit 4 (COX4)* (two proteins derived from the mitochondrial and nuclear genome).[136] Further, higher mitochondrial biogenesis accentuates the expression of proteins required for fatty acid oxidation and increased lipid turnover.[136] Browning effects are also caused by the inhibition of autophagy via PPARγ activation associated with these compounds.[137] White adipose tissue is known to attain brown-like features such as increased β-oxidation and insulin sensitivity when autophagy is suppressed.[138] Adiponectin is secreted by EAT and reduces oxidative stress from the myocardium via activation of AMPK in cardiomyocytes.[139] The activation of PPARγ increased the

expression of adiponectin, resulting in the protection of the heart from oxidative stress.[76] Moreover, adiponectin has been illustrated to promote an anti-inflammatory phenotype of macrophages from subcutaneous fat.[140] Collectively, these findings suggest that PPARγ agonists positively alter the biological processes within EAT in regard to decreased inflammation as well as the white-to-brown transition of the fat depot.

5.3 | AMPK agonists—Metformin

AMP-activated protein kinase (AMPK) acts as a cellular energy sensor.[81] Drugs like metformin activate AMPK and have been shown to reduce EAT thickness, which is thought to occur via enhanced fatty acid oxidation, reduced lipogenesis, and suppression of inflammation. A prospective clinical study investigated the effects of metformin monotherapy over a period of 3 months on 40 type 2 diabetes patients. The participants were prescribed 1000 mg twice a day and EAT thickness was measured echocardiographically post-treatment. The results showed a significant reduction of EAT area.[82] Moreover, this effect was not only limited to adults but was also observed in children, as Güneş et al. investigated the effect of metformin on 30 obese children with insulin resistance. After a 3-month treatment period a significant reduction in EAT area was determined echocardiographically.[83] However, both observational studies have similar weaknesses as they used rather small sample sizes and did not correlate their findings to inflammatory markers.[82,83] Furthermore, literature seems contradictory as observed in a study conducted by Al-Talabany et al.: The study aimed to investigate whether CAD patients without type 2 diabetes exhibit changes in EAT after metformin administration; however MRI measurements of EAT thickness showed no significant differences before and after treatment.[108] Additionally, combining metformin with dapagliflozin has been shown to reduce EAT thickness more rapidly,[84] however, this effect may also be attributed to dapagliflozin. Conclusively, the results highlight the possibility that metformin's effect may depend on the baseline residual volume or insulin sensitivity in individual patients[108] and that other agents probably have a bigger impact on reducing overall EAT volume.[84] Metformin's positive effects extend beyond the total EAT volume as it influences inflammatory expression within the coronary vessels. In a retrospective study involving 547 type 2 diabetes patients, pericoronary adipose tissue was analysed using coronary computed tomography angiography. Patients treated with metformin showed lower CT attenuation in the tissue, indicating lower inflammatory levels which can be correlated to overall coronary inflammation.[141] Since EAT is anatomically located directly on coronary vessels, a similar effect could be assumed.

5.3.1 | Mechanistic pathways of AMPK agonists—Metformin

As stated before, AMPK is a heterodimeric metabolic sensor, activated by different states of metabolic stress such as hypoxia and ischemia.[142] Further it improves fatty oxidation in skeletal muscles by inactivating the enzyme Acetyl-CoA Carboxylase (ACC) via phosphorylation.[143] ACC is responsible for the activation of malonyl-CoA which in turn blocks the activity of Carnitine palmitoyl transferase 1 (CPT1). CPT1 increases β-oxidation in mitochondria.[144] Therefore, CPT1 is activated indirectly by AMPK, resulting in enhanced oxidation of fatty acids.[144] Metformin exerts multiple anti-inflammatory mechanisms in EAT, in part by activating AMPK, which negatively regulates NF-κB signalling. Specifically, metformin reduces phosphorylation and nuclear translocation of NF-κB,[145] thereby decreasing ROS production[85] and downregulating pro-inflammatory cytokines such as IL-6 and TNF-α.[146,147] By modulating upstream activators and downstream effectors of NF-κB, metformin restores adipose tissue homeostasis and mitigates chronic inflammation associated with cardiovascular risk. Moreover, metformin significantly increases PPARγ protein expression, indicating enhanced adiponectin production in EAT.[86] It also affects the responsiveness of adiponectin, as it stimulates the expression of *Adiponectin Receptor 1 (AdripoR1)*.[87] In summary, metformin has a direct anti-inflammatory effect on adipocytes as it upregulates adiponectin and suppresses inflammatory cytokines.[87] Similar to PPARγ agonists, metformin has been demonstrated (in vivo) to decrease M1 macrophage markers such as *CD11c* and shift the macrophage polarization towards the anti-inflammatory M2 type in adipose tissue.[88] Collectively, these findings highlight the possibility of reducing EAT volume in patients with type 2 diabetes which could be caused by increased lipid turnover. However, the principal advantage of metformin has been shown in several mechanisms decreasing chronic low-grade inflammation in adipose tissue.[88]

5.4 | GLP1R agonists

Beyond their glucose-lowering and weight-reducing effects, GLP-1 receptor agonists (GLP-1RAs) exert anti-inflammatory and thermogenic actions in adipose tissue adjacent to the heart. Here, we review drug-specific evidence on GLP-1RAs and EAT, followed by mechanistic insights into potential pathways of action.

5.4.1 | Liraglutide

Liraglutide has been demonstrated (in vitro) to promote a thermogenic program in adipocytes, increasing *UCP1*,[89] mitochondrial respiration[90] and biogenesis, and beige/brown markers in rodent and human adipocytes, with evidence for AMPK–PGC-1α and thyroid hormone Type 2 Iodothyronine Deiodinase (DIO2) involvement (and additive effects with β3-adrenergic stimulation).[91,92] EAT expresses GLP-1R and its expression associates with transcripts for fatty-acid oxidation and white-to-brown differentiation, supporting a depot-specific targetable pathway.[10] In patients on liraglutide, peripheral blood monocyte/macrophage phenotypes have been shown to shift towards M2 with reduced TNF-α and oxidative stress ex vivo, consistent with anti-inflammatory actions that may translate to adipose depots including

EAT.[93] Liraglutide has also been reported to modulate EAT microRNA profiles ex vivo from surgical samples, implicating post-transcriptional control of inflammatory and metabolic pathways in this depot.[94] Echocardiographic and CT/MRI studies show liraglutide reduces cardiac/epicardial fat. A prospective echocardiographic study found a large, rapid reduction in EAT thickness within weeks, out of proportion to early changes in general adiposity.[95] A CT study in type 2 diabetes reported significant decreases in total cardiac adipose tissue with liraglutide; the reduction tracked with weight loss, suggesting both direct and indirect mechanisms.[96] Reviews of EAT in heart failure note that liraglutide-associated EAT reduction correlated with left-ventricular (LV) mass regression, linking local depot remodelling to cardiac structure.[22]

5.4.2 | Semaglutide

Emerging experimental and translational studies have begun to investigate how semaglutide exerts depot-specific actions on epicardial adipose tissue (EAT). In vitro and ex vivo evidence indicates that semaglutide directly modulates EAT adipogenesis and inflammatory signalling. Basdaş and colleagues recently demonstrated in human epicardial adipose progenitor models that semaglutide attenuates pro-inflammatory adipogenesis by downregulating *fatty acid–binding protein 4 (FABP4)* and *secretory phospholipase A2 (sPLA2)*, while concomitantly improving paracrine effects on adjacent atrial cardiomyocytes, suggesting a direct protective crosstalk between treated EAT and the myocardium.[97] Complementary proteomic profiling of adipose tissue exposed to semaglutide has revealed broad downregulation of lipogenic and inflammatory pathways and upregulation of mitochondrial oxidative proteins, underscoring the capacity of GLP-1 receptor activation to reprogram adipose metabolism at the cellular level.[98] Human EAT expresses the GLP-1 receptor itself, and transcriptomic studies of surgical EAT samples show that higher *GLP-1R* expression correlates positively with fatty acid oxidation and white-to-brown differentiation gene programs.[10] These findings provide a mechanistic substrate for the browning phenotype observed in other adipose depots. Indeed, independent in vitro adipocyte culture studies have shown that semaglutide upregulates *UCP1*, *PGC-1α*, and other thermogenic markers, while simultaneously reducing endoplasmic reticulum stress and pro-inflammatory cytokine release, thereby promoting a more oxidative and metabolically flexible adipocyte phenotype.[99] However, the latter study did not specifically investigate EAT; similar mechanisms are however likely at play across visceral fat depots. Ex vivo studies on human EAT explants furthermore demonstrated that semaglutide reduces the secretion of atherothrombotic adipokines such as FABP4, which has been linked to coronary artery disease and arrhythmogenesis, and attenuates paracrine inflammatory signalling towards cardiomyocytes.[100] Such paracrine modulation offers a plausible mechanistic link between semaglutide's local effects in EAT and its clinical cardiovascular benefits.

Clinical observations are congruent with these mechanistic findings. Randomized and observational imaging studies consistently show that semaglutide significantly reduces EAT thickness and volume in patients with type 2 diabetes and obesity.[101] In a 12-week, controlled, parallel-group study of 80 subjects with type 2 diabetes and obesity, both semaglutide (up to 1 mg/week) and dulaglutide (up to 1.5 mg/week) produced statistically significant reductions in ultrasound-measured epicardial adipose tissue (EAT) thickness—roughly a 20% decrease versus baseline—demonstrating a rapid and dose-dependent depot response.[101] The STOP (Semaglutide Treatment effect On coronary atherosclerosis Progression) trial recently provided confirmatory CT imaging evidence that semaglutide not only reduces epicardial adipose tissue (EAT) volume but also favourably modifies coronary plaque characteristics in patients with type 2 diabetes and established coronary artery disease.[102] Notably, in several cohorts, reductions in EAT appear to precede or exceed early changes in systemic adiposity, supporting the concept of depot-specific and potentially weight-independent mechanisms.[102]

5.4.3 | Exenatide

Exenatide has been shown to induce changes in epicardial adipose tissue (EAT) in both experimental and clinical settings. Preclinical studies in rodent and human adipocytes demonstrate that exenatide reduces adipogenic and lipogenic gene expression while enhancing lipolytic and oxidative markers, leading to a less hypertrophic and more metabolically active adipocyte phenotype.[103,104] In rodent models, exenatide-treated visceral adipose depots exhibit increased expression of mitochondrial and browning-related markers, consistent with a more energy-expending phenotype.[103] However, again these studies were not performed directly on EAT and depot-specific effects require further investigation. In a prospective MRI/MRS study of patients with type 2 diabetes and obesity, 6 months of exenatide therapy significantly reduced EAT volume and thickness.[105]

5.4.4 | Tirzepatide

While not a pure GLP-1RA (as it also targets the Glucose-dependent Insulinotropic Polypeptide receptor) tirzepatide engages GLP-1 pathways and is highly relevant. In the SUMMIT CMR substudy (HFpEF with obesity), 52 weeks of tirzepatide reduced left ventricular mass and paracardiac adipose tissue (combined epicardial and pericardial) versus placebo. While dedicated EAT-only quantification was not performed, results imply a likely epicardial component.[106] The parent SUMMIT trial also demonstrated that tirzepatide improves cardiovascular outcomes in obesity-related HFpEF and reduces paracardiac adipose tissue—likely including epicardial fat—supporting the potential for direct or indirect modulation of EAT.[107,148] Mechanistically, tirzepatide's weight-loss–mediated and incretin-mediated anti-inflammatory actions may extend to EAT, but more EAT-specific human imaging and in vitro data are required to confirm direct effects independent of weight change.

5.4.5 | Mechanistic pathways of GLP-1RAs in EAT

At the systemic level, GLP-1RAs improve glucose homeostasis, promote weight loss, enhance insulin sensitivity, and lower circulating inflammatory mediators such as C-reactive protein (CRP) and TNF-α. These effects indirectly influence EAT by altering lipid flux and systemic inflammatory tone, leading to secondary regression of visceral and epicardial fat. However, several lines of evidence indicate that GLP-1RAs also act locally within EAT through direct receptor-mediated mechanisms. GLP-1 receptors are expressed in human EAT.[109] This establishes EAT as a direct target of GLP-1 signalling and provides a molecular basis for depot-specific effects. Experimental studies support these local mechanisms: liraglutide activates AMPK–PGC-1α signalling and increases *UCP1* expression, mitochondrial respiration, and beige/brown markers in rodent and human adipocytes, effects augmented by β_3-adrenergic stimulation.[89–94] Similarly, semaglutide and exenatide enhance oxidative metabolism and thermogenic gene expression while suppressing lipogenic and inflammatory pathways in adipocytes and EAT explants.[97,99,104] In vitro, GLP-1RAs reduce pro-inflammatory adipokines such as FABP4 and sPLA2[97] and shift macrophage polarization towards an M2 anti-inflammatory phenotype.[93] These changes reduce paracrine inflammatory signalling from EAT to adjacent myocardium, potentially mitigating myocardial fibrosis and vascular inflammation.[97] The integration of systemic and local actions likely explains why reductions in EAT volume and inflammation often exceed what would be expected solely from weight loss or improved glycemic control with imaging evidence reinforcing this concept (especially concerning EAT attenuation). Taken together, GLP-1RAs remodel EAT through a combination of systemic metabolic improvement and direct local modulation of adipocyte phenotype, inflammation, and mitochondrial activity. These processes converge to restore a more lipid-rich, anti-inflammatory, and thermogenically competent EAT profile, thereby reducing its pathogenic paracrine influence on the heart and coronary vasculature. Further mechanistic studies using human EAT explants and in vivo imaging biomarkers are warranted to disentangle the relative contributions of systemic versus local effects and to assess potential drug-specific differences across the GLP-1RA class.

5.5 | SGLT2 inhibitors

5.5.1 | Dapagliflozin

Dapagliflozin has been investigated in human EAT explants and paired EAT-derived progenitors, where it improved insulin sensitivity (↑GLUT4 translocation), enhanced adipogenic differentiation capacity, and suppressed pro-inflammatory chemokine/cytokine expression (e.g., *MCP-1/CCL2*, *IL-6*), suggesting a direct anti-inflammatory action on human EAT independent of systemic glycemia.[110] In explant studies using epicardial adipose tissue from patients with coronary artery disease, dapagliflozin significantly reduced the amount of lactate released into the culture medium. Because high lactate output from EAT reflects a glycolytic, pro-inflammatory, and metabolically stressed state, this reduction indicates that dapagliflozin reprograms the depot towards a more oxidative, energy-efficient phenotype.[111] In obese rat models, dapagliflozin reduced leptin release from epicardial and pericardial fat, thereby limiting leptin-driven myocardial remodelling and providing preclinical evidence that it may disrupt harmful EAT–heart crosstalk.[112] Beyond EAT specifically, several rodent and cellular studies show SGLT2i-driven browning programs; for dapagliflozin, recent work in high-fat diet–induced obese mice demonstrated upregulation of canonical browning markers such as *PRDM16* and *UCP1*, along with increased expression of angiogenesis-related genes (e.g., *VEGFA*) and histological evidence of enhanced mitochondrial content.[113] Complementary experiments in 3T3-L1 adipocytes confirmed transcriptional induction of browning and angiogenic regulators, supporting a direct adipocyte-autonomous effect.[113,114] Furthermore, multiple human studies link dapagliflozin to reductions in EAT. Multiple randomized trials showed decreased EAT volume by CT and ultrasound after 6 months of treatment in T2D and obesity, with accompanying improvements in atrial electrophysiology indices.[84,115] More recently, a PET/CT study demonstrated that dapagliflozin lowered EAT thickness and reduced epicardial glucose uptake (^{18}F-FDG), implying metabolic and inflammatory 'cooling' of this depot.[116] However, not all contexts show the same effects: following acute coronary syndrome, one study found EAT thickness increased post-ACS and was not significantly attenuated by short-term dapagliflozin, underscoring disease-stage and timing effects on EAT responsiveness.[117]

5.5.2 | Empagliflozin

In ex vivo studies of human EAT preadipocytes, empagliflozin inhibited cell differentiation, reduced pro-inflammatory cytokine secretion (IL-6, MCP-1), and reduced ROS generation by cardiomyocytes in coculture—indicating improved paracrine adipose–myocardial crosstalk.[118] Again, concrete data on EAT remains scarce while generally effects on visceral fat appear promising: For example, in diet-induced obese mice, empagliflozin promotes fat utilization, WAT browning (↑*UCP1*), and a shift towards anti-inflammatory M2 macrophage polarization, consistent with improved adipose tissue immunometabolism.[119] Whether this effect holds true for EAT will require more thorough investigation. Cardiac magnetic resonance (CMR) studies in patients with heart failure with reduced ejection fraction (HFrEF) provide convergent mechanistic hints. In the EMPA-TROPISM trial (non-diabetic HFrEF), empagliflozin reduced surrogate markers of adverse cardiac remodelling and was accompanied by favourable changes in cardiac adiposity, with reports of quantifiable EAT volume reduction by CMR alongside decreases in inflammatory biomarkers.[120] In T2D with coronary artery disease, the EMPA-HEART CardioLink-6 trial showed a significant reduction in left ventricular mass over 6 months—an effect hypothesized to also involve changes in pericardial/epicardial fat. However, this will require further investigation, as EAT thickness and remodelling were not the primary endpoint of this study.[121] Overall, current clinical data support that empagliflozin

causes EAT reduction in selected populations (particularly HFrEF and T2D) while acknowledging neutral findings in others, likely reflecting differences in disease substrate, baseline EAT burden, and imaging methodology.[22,122]

5.5.3 | Canagliflozin, luseogliflozin and ipragliflozin

Further, less commonly used SGLT2 inhibitors include canagliflozin, luseogliflozin, and ipragliflozin. While preclinical mechanistic data on their effects in EAT remain largely unexplored, scarce clinical evidence suggests beneficial outcomes. In a prospective study of patients with type 2 diabetes, canagliflozin significantly reduced CT-quantified epicardial fat volume over approximately 6 months, accompanied by improvements in metabolic parameters.[123] Similarly, in a single-arm 12-week MRI study of Japanese patients with type 2 diabetes, luseogliflozin significantly decreased epicardial fat volume, and the magnitude of reduction correlated with declines in circulating C-reactive protein, linking depot-specific changes to systemic inflammation.[124] Additionally, in a pilot study of non-obese patients with type 2 diabetes and visceral obesity, ipragliflozin markedly reduced MRI-measured epicardial fat volume over 12 weeks, with reductions correlating with improvements in metabolic and inflammatory markers, indicating potential EAT benefits even outside obese populations.[125] However, evidence on EAT effects of these substances remains scarce and largely unexplored; in-depth investigation of specifically luseogliflozin (commonly used in Japan) would be desirable.

5.5.4 | Mechanistic pathways of SGLTi

SGLT2 inhibitors reduce epicardial adipose tissue by systemically promoting glycosuria-induced calorie and weight loss and improving insulin sensitivity, thereby decreasing adipocyte inflammation and lipid accumulation.[149] Furthermore, adipocyte reprogramming towards thermogenesis ('browning') is a key mechanism: Preclinical studies show that SGLT2 inhibitors enhance *UCP1*, *PRDM16*, and *PGC-1α* expression, promote mitochondrial biogenesis, and increase oxidative phosphorylation in adipocytes, consistent with beige/brown remodelling and elevated lipid oxidation.[150] While most data derive from white adipose tissue, these programs likely generalize to EAT, and are supported by human EAT explant data.[151] Anti-inflammatory and immunometabolic effects, including leptin modulation, constitute another central mechanism. SGLT2 inhibitors reduce inflammatory cytokines and chemokines in EAT explants (e.g., *IL-6*, *MCP-1*)[151] and promote macrophage polarization towards the M2 phenotype, lowering depot inflammation and mitigating paracrine injury to adjacent myocardium and coronary vessels.[110,151,152] Dapagliflozin inhibits leptin production and secretion from EAT through the PI3K/AKT and ERK1/2 pathways in insulin-resistant rats.[113] In co-culture experiments of epicardial adipocytes, cardiomyocytes, and cardiac fibroblasts, this suppression of leptin attenuates leptin-induced cardiac fibrosis via the JAK2-STAT3-ROS-$Na^{+/}K^{+-}$ATPase axis in fibroblasts and reduces leptin-driven cardiomyocyte apoptosis through the JAK2-STAT3-Bcl-2 pathway.[113] Imaging evidence, such as reduced ^{18}F-FDG uptake in EAT with dapagliflozin, further suggests a shift in glucose metabolism of EAT.[116] Systemic metabolic effects also contribute: Glycosuria induced by SGLT2 inhibition lowers circulating insulin levels and improves insulin sensitivity, reducing fatty acid oxidation in EAT.[153] The reduction in insulin and increase in glucagon levels associated with SGLT2 inhibition promote lipolysis and fatty acid oxidation: This shift enhances the utilization of fatty acids as an energy source, promoting adipocyte lipid mobilization and oxidation.[154] Additionally, SGLT2 inhibitors enhance hemodynamic parameters by decreasing preload and afterload, thereby alleviating congestion and further mitigating EAT-derived inflammatory signalling. Clinical trials, including EMPA-TROPISM and EMPA-HEART, have demonstrated that treatment with SGLT2 inhibitors leads to favourable cardiac remodelling and reductions in EAT volume, highlighting the bidirectional benefits between the heart and epicardial fat.[121,155]

While data on the widely used SGLTi empagliflozin and dapagliflozin demonstrate intriguing mechanistic insights, data on less commonly used drugs such as canagliflozin, luseogliflozin, and ipragliflozin remain scarce. Clinical data indicate a systemic effect of lowering pro-inflammatory signalling molecules such as C-reactive protein[125] and lowering of LDL levels,[149] which may indirectly affect EAT in similar manners as empagliflozin and dapagliflozin. However, current meta-analyses also state that evidence on the mechanistics of lesser-known SGLT2i remains scarce and requires further investigation.[149] Contextual factors critically influence EAT outcomes and have to be taken into consideration when analysing these studies. The magnitude and consistency of changes vary according to clinical substrate (e.g., HFpEF versus early T2D), disease stage (e.g., post-ACS), baseline EAT burden, and the imaging modality or segmentation protocol used. Neutral findings in some dapagliflozin or empagliflozin studies likely reflect these variables rather than a lack of class-wide efficacy.

The distinction between systemic and local effects of SGLT2i remains an open question. Clinical studies primarily evaluate systemic parameters such as circulating lipid levels and inflammatory markers,[114,149,153,154] whereas local tissue-specific effects can only be explored through in vivo or in vitro models. Current clinical evidence suggests that SGLT2i reduce EAT volume to an extent that exceeds what would be expected from systemic metabolic improvements alone.[154] Moreover, in vitro studies using EAT explants have demonstrated increased browning of EAT adipocytes with empagliflozin and dapagliflozin,[119] suggesting a potential direct mechanism of action. Further detailed investigation of local adipokine and cytokine signalling within EAT upon treatment with lesser known SGLT2i is of interest, as preliminary preclinical data indicate locally mediated effects that may vary among different SGLT2 inhibitors.

6 | CONCLUDING REMARKS AND FUTURE DIRECTIONS

Pharmacologic modulation of EAT has emerged as a pivotal mechanism through which contemporary glucose- and lipid-lowering

therapies confer cardiovascular improvements (Figure 3, Table 1). Statins, particularly atorvastatin, consistently reduce EAT volume and inflammation by inhibiting NF-κB signalling, shifting macrophage polarization towards an M2 phenotype, and potentially promoting browning via upregulation of thermogenic genes.[11,68,69,126,130,132] PPARγ agonists improve insulin sensitivity within EAT and favour an anti-inflammatory adipokine profile,[74,80] while AMPK activators such as metformin suppress lipogenesis and enhance fatty acid oxidation,[87,146] collectively mitigating depot inflammation. GLP-1 receptor agonists—including liraglutide, semaglutide, and exenatide—directly act on epicardial adipocytes through GLP-1R, inducing browning via UCP1, PGC-1α, and mitochondrial biogenesis, while attenuating pro-inflammatory cytokine secretion and improving paracrine communication with cardiomyocytes.[10,103] Similarly, SGLT2 inhibitors reduce EAT thickness and inflammation through multiple convergent mechanisms: promoting adipocyte browning, enhancing mitochondrial oxidative phosphorylation, lowering leptin, and modulating macrophage polarization and cytokine release towards an anti-inflammatory state.[112,113,118,119,150] Systemic metabolic effects—such as reduced insulin levels, increased fatty acid utilization, and improved hemodynamics—further amplify these depot-specific actions, creating a synergistic anti-inflammatory and cardioprotective environment.[114,149] Ultimately, the discussed pharmacologic classes converge on a shared mechanistic theme: reprogramming EAT from a pro-inflammatory white phenotype towards a thermogenically and metabolically active, anti-inflammatory beige/brown state, thereby exerting cardioprotective benefits for patients. This transition is driven by mitochondrial biogenesis, upregulation of UCP1/PGC-1α/PRDM16, and macrophage-mediated anti-inflammatory remodelling, as summarized in Figure 3.

Collectively, these findings highlight that EAT is a highly plastic and pharmacologically targetable tissue, wherein reductions in thickness, EAT attenuation, inflammatory signalling, and activation of thermogenic pathways may directly influence myocardial remodelling and mitigate cardiovascular risk. Future investigations should seek a more detailed characterization of drug-specific EAT responses—including dose dependence, temporal dynamics, and depot-specific browning—to refine therapeutic strategies that leverage EAT modulation as a mechanistic driver of cardiometabolic benefit. Integrating in vivo/clinical advanced imaging techniques with ex vivo tissue analysis and in vitro molecular and single-cell profiling will be essential to disentangle local tissue effects from systemic metabolic influences and to identify causal pathways linking EAT remodelling to cardiac structural and functional outcomes. Elucidating these multidimensional interactions will not only enhance mechanistic understanding and target identification for novel therapies, but

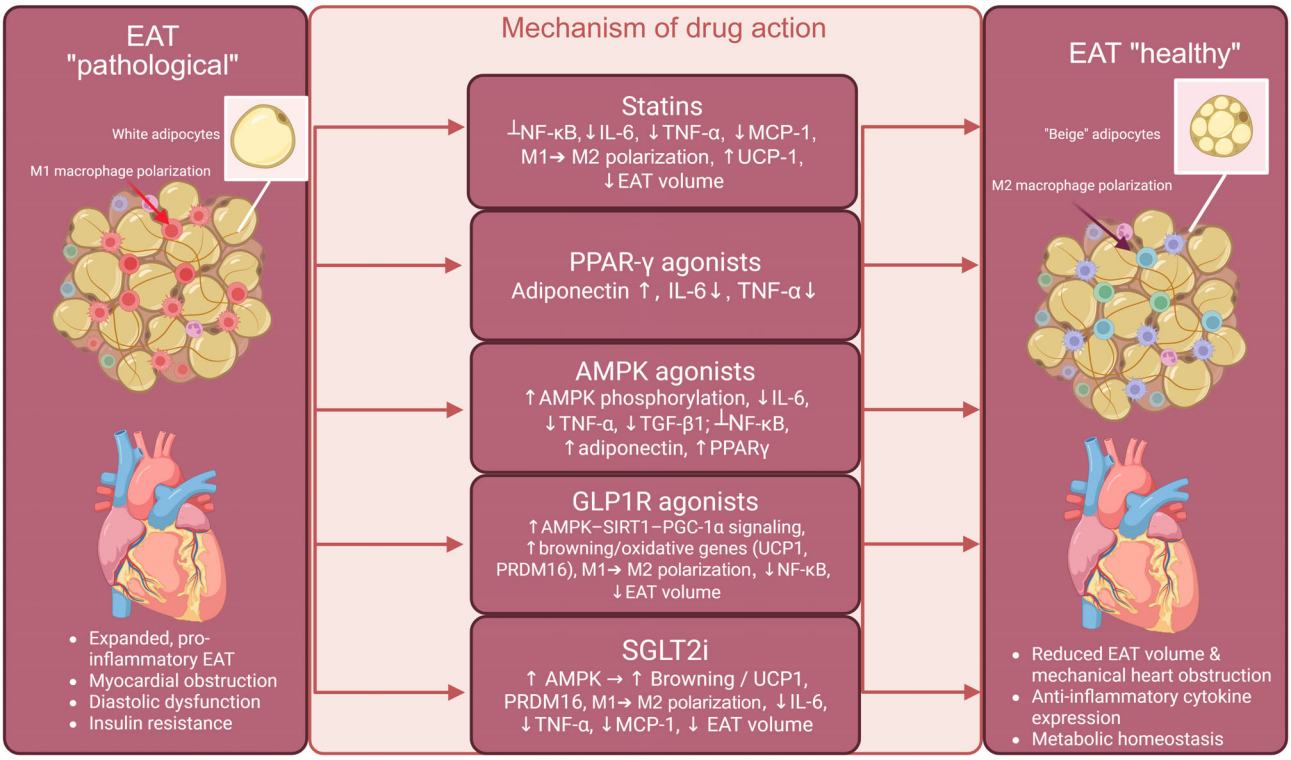

FIGURE 3 Detailed mechanisms by which lipid- and glucose-lowering drugs modulate EAT to improve cardiac health and function. Statins, PPARγ agonists, AMPK agonists, SGLT2i, and GLP1R agonists act on EAT to reduce inflammatory cytokine and adipokine secretion, improve metabolic activity, and promote a phenotypic shift from a pro-inflammatory, 'white', and metabolically dysfunctional state towards a more 'brown/beige', anti-inflammatory, and metabolically active profile. These adaptations restore protective paracrine signalling between EAT and the myocardium, contributing to improved cardiac outcomes. Specific signalling molecules and pathways are depicted within the figure. Created in BioRender. Reingruber, S. (2025) https://BioRender.com/8l77gjo.

also enable clinicians to make more informed and targeted therapeutic decisions aimed at reprogramming EAT towards a metabolically favourable, anti-inflammatory, and cardioprotective phenotype—ultimately translating into cardiovascular benefit and improved quality of life for patients.

AUTHOR CONTRIBUTIONS

Elisabeth Heuboeck designed the review, performed a literature search, and wrote the manuscript. Charnkamal Singh Bhogal assisted with data collection, literature research and manuscript drafting. Markus Mandl revised the manuscript and approved the final version. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors express their sincere gratitude to Dr. Peter Benedikt, Dr. Florian Huber, Univ.-Prof. Dr. Andreas F. Zierer, and the Department of Cardiac and Thoracic Surgery at the Kepler University Hospital Linz for kindly providing the intraoperative image used in this paper. Their support and contribution are greatly appreciated. The authors furthermore wish to acknowledge the cooperation with the Clinical Research Institute for Cardiovascular and Metabolic Diseases, Medical Faculty, Johannes Kepler University Linz, and the great support of Univ.-Prof. Dr. David Bernhard in these ongoing joint research efforts. Open Access funding provided by Johannes Kepler Universitat Linz/KEMÖ.

FUNDING INFORMATION

This research was published with the support of the Open Access Publication Fund of the Johannes Kepler University Linz and the federal state Upper Austria.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70324.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new datasets were generated or analysed during the current study. All data used are available in the published literature and can be accessed through the respective DOIs cited in the references.

ORCID

Elisabeth Heuboeck https://orcid.org/0009-0005-5230-0683
Charnkamal Singh Bhogal https://orcid.org/0009-0001-5247-5839
Markus Mandl https://orcid.org/0000-0002-1039-8994

REFERENCES

1. Talman AH, Psaltis PJ, Cameron JD, Meredith IT, Seneviratne SK, Wong DTL. Epicardial adipose tissue: far more than a fat depot. *Cardiovasc Diagn Ther*. 2014;4(6):416-429. doi:10.3978/j.issn.2223-3652.2014.11.05
2. Iacobellis G, Pistilli D, Gucciardo M, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine*. 2005;29(6):251-255. doi:10.1016/J.CYTO.2004.11.002
3. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol*. 2022;19(9):593-606. doi:10.1038/s41569-022-00679-9
4. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends in Endocrinol Metab*. 2011;22(11):450-457. doi:10.1016/j.tem.2011.07.003
5. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation*. 2003;108(20):2460-2466. doi:10.1161/01.CIR.0000099542.57313.C5
6. Chaowalit N, Lopez-Jimenez F. Epicardial adipose tissue: friendly companion or hazardous neighbour for adjacent coronary arteries? *Eur Heart J*. 2008;29(6):695-697. doi:10.1093/eurheartj/ehm643
7. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. *Nat Rev Endocrinol*. 2015;11(6):363-371. doi:10.1038/nrendo.2015.58
8. Iacobellis G. *Epicardial Adipose Tissue*. Springer Nature Switzerland; 2020 http://www.springer.com/series/7677
9. Nagy L, Tontonoz P, Alvarez JGA, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARγ. *Cell*. 1998;93(2):229-240. doi:10.1016/S0092-8674(00)81574-3
10. Dozio E, Vianello E, Malavazos AE, et al. Epicardial adipose tissue GLP-1 receptor is associated with genes involved in fatty acid oxidation and white-to-brown fat differentiation: A target to modulate cardiovascular risk? *Int J Cardiol*. 2019;292:218-224. doi:10.1016/J.IJCARD.2019.04.039
11. Park JH, Park YS, Kim YJ, et al. Effects of statins on the Epicardial fat thickness in patients with coronary artery stenosis underwent percutaneous coronary intervention: comparison of atorvastatin with simvastatin/ezetimibe. *J Cardiovasc Ultrasound*. 2010;18(4):121. doi:10.4250/jcu.2010.18.4.121
12. Bao Y, Hu Y, Shi M, Zhao Z. SGLT2 inhibitors reduce epicardial adipose tissue more than GLP −1 agonists or exercise interventions in patients with type 2 diabetes mellitus and/or obesity: A systematic review and network meta-analysis. *Diabetes Obes Metab*. 2025;27(3):1096-1112. doi:10.1111/dom.16107
13. Sacks H, Symonds ME. Anatomical locations of human Brown adipose tissue. *Diabetes*. 2013;62(6):1783-1790. doi:10.2337/db12-1430
14. La V, Nair V, Sunny S, Benharash P, Thankam FG. Epicardial adipocytes in cardiac pathology and healing. *Cardiovasc Drugs Ther*. 2024. doi:10.1007/s10557-024-07637-2
15. Sacks HS, Fain JN, Holman B, et al. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: Epicardial fat functioning as brown fat. *J Clin Endocrinol Metabol*. 2009;94(9):3611-3615. doi:10.1210/jc.2009-0571
16. Townsend K, Tseng YH. Brown adipose tissue. *Adipocyte*. 2012;1(1):13-24. doi:10.4161/adip.18951
17. Chechi K, Blanchard PG, Mathieu P, Deshaies Y, Richard D. Brown fat like gene expression in the epicardial fat depot correlates with circulating HDL-cholesterol and triglycerides in patients with coronary artery disease. *Int J Cardiol*. 2013;167(5):2264-2270. doi:10.1016/J.IJCARD.2012.06.008
18. Ho E, Shimada Y. Formation of the epicardium studied with the scanning electron microscope. *Dev Biol*. 1978;66(2):579-585. doi:10.1016/0012-1606(78)90263-4
19. Doukbi E, Soghomonian A, Sengenès C, et al. Browning epicardial adipose tissue: friend or foe? *Cells*. 2022;11(6):991. doi:10.3390/cells11060991

20. Chechi K, Vijay J, Voisine P, et al. UCP1 expression–associated gene signatures of human epicardial adipose tissue. *JCI Insight*. 2019;4(8): e123618. doi:10.1172/jci.insight.123618
21. Cook L, Perry M, Hill A, Thorpe J. Methods to model epicardial adipose tissue-mediated atrial fibrillation. *NPJ Cardiovasc Health*. 2025; 2(1):29. doi:10.1038/s44325-025-00065-7
22. Cho DH, Park SM. Epicardial adipose tissue and heart failure, friend or foe? *Diabetes Metab J*. 2024;48(3):373-384. doi:10.4093/dmj.2023.0190
23. Villarreal-Molina MT, Antuna-Puente B. Adiponectin: anti-inflammatory and cardioprotective effects. *Biochimie*. 2012;94(10): 2143-2149. doi:10.1016/j.biochi.2012.06.030
24. Aljafary MA, Al-Suhaimi EA. Adiponectin system (rescue hormone): the missing link between metabolic and cardiovascular diseases. *Pharmaceutics*. 2022;14(7):1430. doi:10.3390/pharmaceutics14071430
25. Toczylowski K, Hirnle T, Harasiuk D, et al. Plasma concentration and expression of adipokines in epicardial and subcutaneous adipose tissue are associated with impaired left ventricular filling pattern. *J Transl Med*. 2019;17(1):310. doi:10.1186/s12967-019-2060-7
26. Du Y, Ji Q, Cai L, et al. Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. *Cardiovasc Diabetol*. 2016;15(1):90. doi:10.1186/s12933-016-0406-5
27. D'Marco L, Puchades MJ, Gorriz JL, et al. Epicardial adipose tissue, adiponectin and leptin: A potential source of cardiovascular risk in chronic kidney disease. *Int J Mol Sci*. 2020;21(3):978. doi:10.3390/ijms21030978
28. Sacks HS, Fain JN. Human epicardial adipose tissue: A review. *Am Heart J*. 2007;153(6):907-917. doi:10.1016/j.ahj.2007.03.019
29. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. *Obes Rev*. 2007;8(3):253-261. doi:10.1111/j.1467-789X.2006.00293.x
30. Iacobellis G, Malavazos AE, Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol*. 2011;43(12):1651-1654. doi:10.1016/J.BIOCEL.2011.09.006
31. Sharma S, Adrogue JV, Golfman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J*. 2004;18(14):1692-1700. doi:10.1096/fj.04-2263com
32. Greulich S, Maxhera B, Vandenplas G, et al. Secretory products from Epicardial adipose tissue of patients with type 2 diabetes mellitus induce Cardiomyocyte dysfunction. *Circulation*. 2012;126(19):2324-2334. doi:10.1161/CIRCULATIONAHA.111.039586
33. Chechi K, Richard D. Thermogenic potential and physiological relevance of human epicardial adipose tissue. *Int J Obes Suppl*. 2015; 5(S1):S28-S34. doi:10.1038/ijosup.2015.8
34. Kankaanpää M, Lehto HR, Pärkkä JP, et al. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. *J Clin Endocrinol Metabol*. 2006;91(11):4689-4695. doi:10.1210/jc.2006-0584
35. Wu Y, Zhang A, Hamilton DJ, Deng T. Epicardial fat in the maintenance of cardiovascular health. *Methodist Debakey Cardiovasc J*. 2017;13(1):20. doi:10.14797/mdcj-13-1-20
36. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. 'Browning' the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol*. 2017;228:265-274. doi:10.1016/j.ijcard.2016.11.074
37. Iacobellis G. Aging effects on Epicardial adipose tissue. *Front Aging*. 2021;2:666260. doi:10.3389/fragi.2021.666260
38. Kotha S, Plein S, Greenwood JP, Levelt E. Role of epicardial adipose tissue in diabetic cardiomyopathy through the lens of cardiovascular magnetic resonance imaging—a narrative review. *Ther Adv Endocrinol Metab*. 2024;15:20420188241229540. doi:10.1177/20420188241229540
39. Moreno-Santos I, Pérez-Belmonte LM, Macías-González M, et al. Type 2 diabetes is associated with decreased PGC1α expression in epicardial adipose tissue of patients with coronary artery disease. *J Transl Med*. 2016;14(1):243. doi:10.1186/s12967-016-0999-1
40. Patel KHK, Hwang T, Se Liebers C, Ng FS. Epicardial adipose tissue as a mediator of cardiac arrhythmias. *Am J Physiol Heart Circ Physiol*. 2022;322(2):H129-H144. doi:10.1152/ajpheart.00565.2021
41. Janssen-Telders C, Eringa EC, de Groot JR, de Man FS, Handoko ML. The role of epicardial adipose tissue remodelling in heart failure with preserved ejection fraction. *Cardiovasc Res*. 2025; 121(6):860-870. doi:10.1093/cvr/cvaf056
42. Song Y, Tan Y, Deng M, et al. Epicardial adipose tissue, metabolic disorders, and cardiovascular diseases: recent advances classified by research methodologies. *MedComm*. 2023;4(6):e413. doi:10.1002/mco2.413
43. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: A new method for visceral adipose tissue prediction. *Obes Res*. 2003;11(2):304-310. doi:10.1038/oby.2003.45
44. Mahabadi AA, Massaro JM, Rosito GA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J*. 2008;30(7):850-856. doi:10.1093/eurheartj/ehn573
45. Goeller M, Achenbach S, Marwan M, et al. Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects. *J Cardiovasc Comput Tomogr*. 2018;12(1):67-73. doi:10.1016/j.jcct.2017.11.007
46. Klüner LV, Oikonomou EK, Antoniades C. Assessing cardiovascular risk by using the fat attenuation index in coronary CT angiography. *Radiol: Cardiothorac Imaging*. 2021;3(1):e200563. doi:10.1148/ryct.2021200563
47. Hemaya M, Hemaya M, Habeeb A. The risks associated with computed tomography scans: an assessment of the readability and reliability of online text available for patient Information and guidance. *Cureus*. 2022;14(10):e30758. doi:10.7759/cureus.30758
48. Rado SD, Lorbeer R, Gatidis S, et al. MRI-based assessment and characterization of epicardial and paracardial fat depots in the context of impaired glucose metabolism and subclinical left-ventricular alterations. *Br J Radiol*. 2019;92(1096):20180562. doi:10.1259/bjr.20180562
49. Flüchter S, Haghi D, Dinter D, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. *Obesity*. 2007;15(4):870-878. doi:10.1038/oby.2007.591
50. Rossi VA, Gruebler M, Monzo L, Galluzzo A, Beltrami M. The different pathways of Epicardial adipose tissue across the heart failure phenotypes: from pathophysiology to therapeutic target. *Int J Mol Sci*. 2023;24(7):6838. doi:10.3390/ijms24076838
51. Langheim S, Dreas L, Veschini L, et al. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. *Am J Physiol Heart Circ Physiol*. 2010;298: 746-753. doi:10.1152/ajpheart.00617.2009
52. Yang X, Feng C, Feng J. Epicardial adipose tissue and diabetic cardiomyopathy. *J Cardiovasc Pharmacol Ther*. 2023;28:28. doi:10.1177/10742484231151820
53. Kubota T, Miyagishima M, Frye CS, et al. Overexpression of tumor necrosis factor- α activates both anti- and pro-apoptotic pathways in the myocardium. *J Mol Cell Cardiol*. 2001;33(7):1331-1344. doi:10.1006/jmcc.2001.1393
54. Chen Z, Qian J, Ma J, et al. TNF-α-induced cardiomyocyte apoptosis contributes to cardiac dysfunction after coronary microembolization in mini-pigs. *J Cell Mol Med*. 2014;18(10):1953-1963. doi:10.1111/jcmm.12342
55. Karampetsou N, Bletsa E, Oikonomou E, et al. Resistin and ICAM-1 as highly expessed proteins in epicardial adipose tissue. *Atherosclerosis*. 2020;315:e121. doi:10.1016/j.atherosclerosis.2020.10.370
56. Jolfayi AG, Beheshti AT, Hosseini SM, et al. Epicardial adipose tissue features as a biomarker and therapeutic target in coronary artery disease. *Sci Rep*. 2025;15(1):14786. doi:10.1038/s41598-025-99600-w

57. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. *Am J Cardiol*. 2004;94(8):1084-1087. doi:10.1016/j.amjcard.2004.06.075
58. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int J Cardiol*. 2007;115(2):272-273. doi:10.1016/j.ijcard.2006.04.016
59. Shimabukuro M, Hirata Y, Tabata M, et al. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2013;33(5):1077-1084. doi:10.1161/ATVBAHA.112.300829
60. Hirata Y, Tabata M, Kurobe H, et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J Am Coll Cardiol*. 2011;58(3):248-255. doi:10.1016/J.JACC.2011.01.048
61. Doesch C, Haghi D, Flüchter S, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson*. 2010;12:40.
62. van Woerden G, van Veldhuisen DJ, Manintveld OC, et al. Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail*. 2022;15(3):e009238. doi:10.1161/CIRCHEARTFAILURE.121.009238
63. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020;8(8):657-666. doi:10.1016/J.JCHF.2020.04.016
64. Gorica E, Geiger MA, Di Venanzio L, et al. Cardiometabolic heart failure with preserved ejection fraction: from molecular signatures to personalized treatment. *Cardiovasc Diabetol*. 2025;24(1):265. doi:10.1186/s12933-025-02774-w
65. Iacobellis G. Coronary artery disease and epicardial adipose tissue. *Epicardial Adipose Tissue*. Springer International Publishing; 2020:77-90. doi:10.1007/978-3-030-40570-0_8
66. Berg G, Barchuk M, Lobo M, Nogueira JP. Effect of glucagon-like peptide-1 (GLP-1) analogues on epicardial adipose tissue: A meta-analysis. *Diabetes Metab Syndr Clin Res Rev*. 2022;16(7):102562. doi:10.1016/j.dsx.2022.102562
67. Raggi P, Gadiyaram V, Zhang C, Chen Z, Lopaschuk G, Stillman AE. Statins reduce Epicardial adipose tissue attenuation independent of lipid lowering: A potential pleiotropic effect. *J Am Heart Assoc*. 2019;8(12):e013104. doi:10.1161/JAHA.119.013104
68. Walker ME, Matthan NR, Solano-Aguilar G, et al. A Western-type dietary pattern and atorvastatin induce epicardial adipose tissue interferon signaling in the Ossabaw pig. *J Nutr Biochem*. 2019;67:212-218. doi:10.1016/j.jnutbio.2019.02.003
69. Soucek F, Covassin N, Singh P, et al. Effects of atorvastatin (80 mg) therapy on quantity of epicardial adipose tissue in patients undergoing pulmonary vein isolation for atrial fibrillation. *Am J Cardiol*. 2015;116(9):1443-1446. doi:10.1016/j.amjcard.2015.07.067
70. Kauerova S, Bartuskova H, Muffova B, et al. Statins directly influence the polarization of adipose tissue macrophages: A role in chronic inflammation. *Biomedicine*. 2021;9(2):211. doi:10.3390/biomedicines9020211
71. Alexopoulos N, Melek BH, Arepalli CD, et al. Effect of intensive versus moderate lipid-lowering therapy on epicardial adipose tissue in hyperlipidemic post-menopausal women. *J Am Coll Cardiol*. 2013;61(19):1956-1961. doi:10.1016/j.jacc.2012.12.051
72. Jo EA, Wu SS, Han HR, Park JJ, Heo JH. Synergistic effects of drug and aerobic exercise on endothelial function and epicardial fat thickness in patients with hypertension and dyslipidemia. *Kosin Medical Journal*. 2025;40(1):31-40. doi:10.7180/kmj.24.137
73. Zhou Y, Tian F, Wang J, et al. Efficacy study of olmesartan medoxomil on coronary atherosclerosis progression and epicardial adipose tissue volume reduction in patients with coronary atherosclerosis detected by coronary computed tomography angiography: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):10. doi:10.1186/s13063-015-1097-z
74. Grosso AF, de Oliveira SF, Higuchi M d L, Favarato D, Dallan LA d O, da Luz PL. Synergistic anti-inflammatory effect: simvastatin and pioglitazone reduce inflammatory markers of plasma and epicardial adipose tissue of coronary patients with metabolic syndrome. *Diabetol Metab Syndr*. 2014;6(1):47. doi:10.1186/1758-5996-6-47
75. Balaz M, Wolfrum C. Statins: benefits and risks revisited. *Aging*. 2019;11(13):4300-4302. doi:10.18632/aging.102056
76. Sacks HS, Fain JN, Cheema P, et al. Inflammatory genes in Epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes. *Diabetes Care*. 2011;34(3):730-733. doi:10.2337/dc10-2083
77. Permana PA, Zhang W, Wabitsch M, Fischer-Posovszky P, Duckworth WC, Reaven PD. Pioglitazone reduces inflammatory responses of human adipocytes to factors secreted by monocytes/-macrophages. *Am J Physiol Endocrinol Metab*. 2009;296(5):E1076-E1084. doi:10.1152/ajpendo.91013.2008
78. Permana PA, Menge C, Reaven PD. Macrophage-secreted factors induce adipocyte inflammation and insulin resistance. *Biochem Biophys Res Commun*. 2006;341(2):507-514. doi:10.1016/j.bbrc.2006.01.012
79. Moody AJ, Molina-Wilkins M, Clarke GD, et al. Pioglitazone reduces epicardial fat and improves diastolic function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2023;25(2):426-434. doi:10.1111/dom.14885
80. Distel E, Penot G, Cadoudal T, Balguy I, Durant S, Benelli C. Early induction of a brown-like phenotype by rosiglitazone in the epicardial adipose tissue of fatty Zucker rats. *Biochimie*. 2012;94(8):1660-1667. doi:10.1016/j.biochi.2012.04.014
81. Hardie DG. AMP-activated protein kinase—an energy sensor that regulates all aspects of cell function. *Genes Dev*. 2011;25(18):1895-1908. doi:10.1101/gad.17420111
82. Ziyrek M, Kahraman S, Ozdemir E, Dogan A. Metformin monotherapy significantly decreases epicardial adipose tissue thickness in newly diagnosed type 2 diabetes patients. *Rev Port Cardiol*. 2019;38(6):419-423. doi:10.1016/j.repc.2018.08.010
83. Güneş H, Güneş H, Özmen Ş, Çelik E, Temiz F. Effects of metformin on epicardial adipose tissue and atrial electromechanical delay of obese children with insulin resistance. *Cardiol Young*. 2020;30(10):1429-1432. doi:10.1017/S1047951120002103
84. Iacobellis G, Gra-Menendez S. Effects of Dapagliflozin on Epicardial fat thickness in patients with type 2 diabetes and obesity. *Obesity*. 2020;28(6):1068-1074. doi:10.1002/oby.22798
85. Morgan MJ, Liu Z g. Crosstalk of reactive oxygen species and NF-κB signaling. *Cell Res*. 2011;21(1):103-115. doi:10.1038/cr.2010.178
86. Su JR, Lu ZH, Su Y, et al. Relationship of serum adiponectin levels and metformin therapy in patients with type 2 diabetes. *Horm Metab Res*. 2016;48(2):92-98. doi:10.1055/s-0035-1569287
87. Li B, Po SS, Zhang B, et al. Metformin regulates adiponectin signalling in epicardial adipose tissue and reduces atrial fibrillation vulnerability. *J Cell Mol Med*. 2020;24(14):7751-7766. doi:10.1111/jcmm.15407
88. Jing Y, Wu F, Li D, Yang L, Li Q, Li R. Metformin improves obesity-associated inflammation by altering macrophages polarization. *Mol Cell Endocrinol*. 2018;461:256-264. doi:10.1016/j.mce.2017.09.025
89. Zhang N, Zhou H, Xu Y, et al. Liraglutide promotes UCP1 expression and lipolysis of adipocytes by promoting the secretion of irisin from skeletal muscle cells. *Mol Cell Endocrinol*. 2024;588:112225. doi:10.1016/j.mce.2024.112225
90. Vaittinen M, Ilha M, Herbers E, et al. Liraglutide demonstrates a therapeutic effect on mitochondrial dysfunction in human SGBS adipocytes in vitro. *Diabetes Res Clin Pract*. 2023;199:110635. doi:10.1016/j.diabres.2023.110635

91. Oliveira FCB, Bauer EJ, Ribeiro CM, et al. Liraglutide activates type 2 deiodinase and enhances β3-adrenergic-induced thermogenesis in mouse adipose tissue. *Front Endocrinol (Lausanne)*. 2022;12:12. doi:10.3389/fendo.2021.803363
92. Zhu E, Yang Y, Zhang J, et al. Liraglutide suppresses obesity and induces brown fat-like phenotype via soluble Guanylyl cyclase mediated pathway *in vivo* and *in vitro*. *Oncotarget*. 2016;7(49):81077-81089. doi:10.18632/oncotarget.13189
93. Bułdak Ł, Bołdys A, Skudrzyk E, Machnik G, Okopień B. Liraglutide therapy in obese patients alters macrophage phenotype and decreases their tumor necrosis factor alpha release and oxidative stress markers—A pilot study. *Metabolites*. 2024;14(10):554. doi:10.3390/metabo14100554
94. Iacobellis G, Goldberger JJ, Lamelas J, et al. Liraglutide effects on epicardial adipose tissue micro-RNAs and intra-operative glucose control. *Nutr Metab Cardiovasc Dis*. 2025;35(2):103726. doi:10.1016/j.numecd.2024.08.019
95. Iacobellis G, Mohseni M, Bianco SD, Banga PK. Liraglutide causes large and rapid epicardial fat reduction. *Obesity*. 2017;25(2):311-316. doi:10.1002/oby.21718
96. Rasmussen IKB, Zobel EH, Ripa RS, et al. Liraglutide reduces cardiac adipose tissue in type 2 diabetes: A secondary analysis of the <scp>LIRAFLAME</scp> randomized <scp>placebo-controlled</scp> trial. *Diabetes Obes Metab*. 2021;23(12):2651-2659. doi:10.1111/dom.14516
97. Basdas R, Martínez-Cereijo JM, Fernández ÁL, et al. Semaglutide modulates proinflammatory epicardial adipogenesis with paracrine effects on hiPSC-atrial cardiomyocytes. *JACC Basic Transl Sci*. 2025;10(9):101277. doi:10.1016/j.jacbts.2025.03.009
98. Zhu R, Chen S. Proteomic analysis reveals semaglutide impacts lipogenic protein expression in epididymal adipose tissue of obese mice. *Front Endocrinol (Lausanne)*. 2023;14:14. doi:10.3389/fendo.2023.1095432
99. Martins FF, Marinho TS, Cardoso LEM, et al. Semaglutide (GLP-1 receptor agonist) stimulates browning on subcutaneous fat adipocytes and mitigates inflammation and endoplasmic reticulum stress in visceral fat adipocytes of obese mice. *Cell Biochem Funct*. 2022;40(8):903-913. doi:10.1002/cbf.3751
100. García-Vega D, Sánchez-López D, Rodríguez-Carnero G, et al. Semaglutide modulates prothrombotic and atherosclerotic mechanisms, associated with epicardial fat, neutrophils and endothelial cells network. *Cardiovasc Diabetol*. 2024;23(1):1. doi:10.1186/s12933-023-02096-9
101. Iacobellis G, Villasante Fricke AC. Effects of semaglutide versus dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity. *J Endocr Soc*. 2020;4(4):bvz042. doi:10.1210/jendso/bvz042
102. Manubolu VS, Lakshmanan S, Kinninger A, et al. Effect of semaglutide on epicardial adipose tissue in type 2 diabetes. *J Am Coll Cardiol*. 2024;84(9):865-867. doi:10.1016/j.jacc.2024.05.065
103. Xu F, Lin B, Zheng X, et al. GLP-1 receptor agonist promotes brown remodelling in mouse white adipose tissue through SIRT1. *Diabetologia*. 2016;59(5):1059-1069. doi:10.1007/s00125-016-3896-5
104. Koldemir Gündüz M, Kaymak G, Kanbur E, Berikten D, Şener H. Exenatide increases CTRP3 gene expression in adipose cells by inhibiting adipogenesis and induces apoptosis. *Toxicol in Vitro*. 2022;85:105479. doi:10.1016/j.tiv.2022.105479
105. Dutour A, Abdesselam I, Ancel P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. *Diabetes Obes Metab*. 2016;18(9):882-891. doi:10.1111/dom.12680
106. Kramer CM, Borlaug BA, Zile MR, et al. Tirzepatide reduces LV mass and paracardiac adipose tissue in obesity-related heart failure. *J Am Coll Cardiol*. 2025;85(7):699-706. doi:10.1016/j.jacc.2024.11.001
107. Bin Abdul Malik MH, Khan NN, Chowdhari MJ, et al. Evaluating the impact of Tirzepatide on clinical outcomes in patients with heart failure. *Cureus*. 2025;17(4):e82118. doi:10.7759/cureus.82118
108. Al-Talabany S, Mohan M, Weir-McCall J, et al. Effect of metformin on epicardial adipose tissue in patients with coronary artery disease without diabetes: A cardiac MRI substudy of the MET-remodel trial. *Obes Med*. 2021;24:100349. doi:10.1016/j.obmed.2021.100349
109. Baggio LL, Yusta B, Mulvihill EE, et al. GLP-1 receptor expression within the human heart. *Endocrinology*. 2018;159(4):1570-1584. doi:10.1210/en.2018-00004
110. Díaz-Rodríguez E, Agra RM, Fernández ÁL, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res*. 2018;114(2):336-346. doi:10.1093/cvr/cvx186
111. Couselo-Seijas M, Agra-Bermejo RM, Fernández AL, et al. High released lactate by epicardial fat from coronary artery disease patients is reduced by dapagliflozin treatment. *Atherosclerosis*. 2020;292:60-69. doi:10.1016/j.atherosclerosis.2019.11.016
112. Luo C, Zheng T, Tian G. Dapagliflozin attenuates epicardial adipose tissue-derived leptin-induced myocardial remodeling in obese rats. *J Am Coll Cardiol*. 2023;81(8):375. doi:10.1016/S0735-1097(23)00819-7
113. Xiang L, Liu M, Xiang G, et al. Dapagliflozin promotes white adipose tissue browning though regulating angiogenesis in high fat induced obese mice. *BMC Pharmacol Toxicol*. 2024;25(1):26. doi:10.1186/s40360-024-00747-5
114. Morciano C, Gugliandolo S, Capece U, et al. SGLT2 inhibition and adipose tissue metabolism: current outlook and perspectives. *Cardiovasc Diabetol*. 2024;23(1):449. doi:10.1186/s12933-024-02539-x
115. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol*. 2018;17(1):6. doi:10.1186/s12933-017-0658-8
116. Cinti F, Leccisotti L, Sorice GP, et al. Dapagliflozin treatment is associated with a reduction of epicardial adipose tissue thickness and epicardial glucose uptake in human type 2 diabetes. *Cardiovasc Diabetol*. 2023;22(1):349. doi:10.1186/s12933-023-02091-0
117. Macías-Cervantes HE, Martínez-Ramírez DB, Hinojosa-Gutiérrez LR, Córdova-Silva DA, Rios-Muñoz JA. Effect of dapagliflozin on epicardial fat volume in patients with acute coronary syndrome assessed by computed tomography. *Curr Probl Cardiol*. 2024;49(2):102213. doi:10.1016/j.cpcardiol.2023.102213
118. Takano M, Kondo H, Harada T, et al. Empagliflozin suppresses the differentiation/maturation of human epicardial preadipocytes and improves paracrine secretome profile. *JACC Basic Transl Sci*. 2023;8(9):1081-1097. doi:10.1016/j.jacbts.2023.05.007
119. Xu L, Nagata N, Nagashimada M, et al. SGLT2 inhibition by Empagliflozin promotes fat utilization and Browning and Attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. *EBioMedicine*. 2017;20:137-149. doi:10.1016/j.ebiom.2017.05.028
120. Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Mechanistic insights of Empagliflozin in nondiabetic patients with HFrEF. *JACC Heart Fail*. 2021;9(8):578-589. doi:10.1016/j.jchf.2021.04.014
121. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation*. 2019;140(21):1693-1702. doi:10.1161/CIRCULATIONAHA.119.042375
122. Hsu JC, Wang CY, Su MYM, Lin LY, Yang WS. Effect of empagliflozin on cardiac function, adiposity, and diffuse fibrosis in patients with type 2 diabetes mellitus. *Sci Rep*. 2019;9(1):15348. doi:10.1038/s41598-019-51949-5
123. Yagi S, Hirata Y, Ise T, et al. Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2017;9(1):78. doi:10.1186/s13098-017-0275-4

124. Bouchi R, Terashima M, Sasahara Y, et al. Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: a pilot study. *Cardiovasc Diabetol*. 2017;16(1):32. doi:10.1186/s12933-017-0516-8
125. Fukuda T, Bouchi R, Terashima M, et al. Ipragliflozin reduces Epicardial fat accumulation in non-obese type 2 diabetic patients with visceral obesity: A pilot study. *Diabetes Ther*. 2017;8(4):851-861. doi:10.1007/s13300-017-0279-y
126. Jamialahmadi T, Simental-Mendia LE, Eid AH, et al. Efficacy of statin therapy in reducing epicardial adipose tissue: a systematic review and meta-analysis. *Arch Med Sci*. 2024;20(3):997-1001. doi:10.5114/aoms/189575
127. Myasoedova VA, Parisi V, Moschetta D, et al. Efficacy of cardiometabolic drugs in reduction of epicardial adipose tissue: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2023;22(1):23. doi:10.1186/s12933-023-01738-2
128. A SA, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in Atherogenesis: molecular mechanisms and lessons from the recent clinical trials. *Curr Pharm Des*. 2012;18(11):1519-1530. doi:10.2174/138161212799504803
129. Koushki K, Shahbaz SK, Mashayekhi K, et al. Anti-inflammatory action of statins in cardiovascular disease: the role of inflammasome and toll-like receptor pathways. *Clin Rev Allergy Immunol*. 2021;60(2):175-199. doi:10.1007/s12016-020-08791-9
130. Mollazadeh H, Tavana E, Fanni G, et al. Effects of statins on mitochondrial pathways. *J Cachexia Sarcopenia Muscle*. 2021;12(2):237-251. doi:10.1002/jcsm.12654
131. Park HS, Jang JE, Ko MS, et al. Statins increase mitochondrial and Peroxisomal fatty acid oxidation in the liver and prevent non-alcoholic Steatohepatitis in mice. *Diabetes Metab J*. 2016;40(5):376-385. doi:10.4093/dmj.2016.40.5.376
132. Sheridan A, Wheeler-Jones CPD, Gage MC. The immunomodulatory effects of statins on macrophages. *Ther Immunol*. 2022;2(2):317-343. doi:10.3390/immuno2020021
133. Machado SA, Pasquarelli-do-Nascimento G, da Silva DS, et al. Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. *Nutr Metab (Lond)*. 2022;19(1):61. doi:10.1186/s12986-022-00694-0
134. Felder M, Maushart CI, Gashi G, et al. Fluvastatin reduces glucose tolerance in healthy young individuals independently of cold induced BAT activity. *Front Endocrinol (Lausanne)*. 2021;12:12. doi:10.3389/fendo.2021.765807
135. Rohm TV, Castellani Gomes Dos Reis F, Isaac R, et al. Adipose tissue macrophages secrete small extracellular vesicles that mediate rosiglitazone-induced insulin sensitization. *Nat Metab*. 2024;6(5):880-898. doi:10.1038/s42255-024-01023-w
136. Li Y, Zheng W, Li X, et al. The autophagic regulation of rosiglitazone-promoted adipocyte browning. *Front Pharmacol*. 2024;15:15. doi:10.3389/fphar.2024.1412520
137. Singh R, Xiang Y, Wang Y, et al. Autophagy regulates adipose mass and differentiation in mice. *J Clin Invest*. 2009;119(11):3329-3339. doi:10.1172/JCI39228
138. Jeon YH, He M, Austin J, Shin H, Pfleger J, Abdellatif M. Adiponectin enhances the bioenergetics of cardiac myocytes via an AMPK- and succinate dehydrogenase-dependent mechanism. *Cell Signal*. 2021;78:109866. doi:10.1016/j.cellsig.2020.109866
139. Antonopoulos AS, Margaritis M, Verheule S, et al. Mutual regulation of epicardial adipose tissue and myocardial redox state by PPAR-γ/adiponectin signalling. *Circ Res*. 2016;118(5):842-855. doi:10.1161/CIRCRESAHA.115.307856
140. Ohashi K, Parker JL, Ouchi N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem*. 2010;285(9):6153-6160. doi:10.1074/jbc.M109.088708
141. Liu Y, Dong Y, Wang X, Xu X. Association between metformin treatment and coronary artery inflammation based on pericoronary adipose tissue attenuation in type 2 diabetes mellitus patients. *J Clin Hypertens*. 2024;26(4):330-337. doi:10.1111/jch.14777
142. Young LH, Li J, Baron SJ, Russell RR. AMP-activated protein kinase: A key stress signaling pathway in the heart. *Trends Cardiovasc Med*. 2005;15(3):110-118. doi:10.1016/j.tcm.2005.04.005
143. Dagher Z, Ruderman N, Tornheim K, Ido Y. Acute regulation of fatty acid oxidation and AMP-activated protein kinase in human umbilical vein endothelial cells. *Circ Res*. 2001;88(12):1276-1282. doi:10.1161/hh1201.092998
144. Long YC. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest*. 2006;116(7):1776-1783. doi:10.1172/JCI29044
145. Hattori Y, Suzuki K, Hattori S, Kasai K. Metformin inhibits cytokine-induced nuclear factor κB activation via AMP-activated protein kinase activation in vascular endothelial cells. *Hypertension*. 2006;47(6):1183-1188. doi:10.1161/01.HYP.0000221429.94591.72
146. Moreno-Navarrete JM, Ortega FJ, Rodríguez-Hermosa JI, et al. OCT1 expression in adipocytes could contribute to increased metformin action in obese subjects. *Diabetes*. 2011;60(1):168-176. doi:10.2337/db10-0805
147. dela Paz NG, Simeonidis S, Leo C, Rose DW, Collins T. Regulation of NF-κB-dependent gene expression by the POU domain transcription factor Oct-1. *J Biol Chem*. 2007;282(11):8424-8434. doi:10.1074/jbc.M606923200
148. Packer M, Zile MR, Kramer CM, Murakami M, Ou Y, Borlaug BA. Interplay of chronic kidney disease and the effects of Tirzepatide in patients with heart failure, preserved ejection fraction, and obesity. *J Am Coll Cardiol*. 2025;85(18):1721-1735. doi:10.1016/j.jacc.2025.03.009
149. Masson W, Lavalle-Cobo A, Nogueira JP. Effect of SGLT2-inhibitors on epicardial adipose tissue: A meta-analysis. *Cells*. 2021;10(8):2150. doi:10.3390/cells10082150
150. Xu L, Xu C, Liu X, et al. Empagliflozin induces white adipocyte Browning and Modulates mitochondrial dynamics in KK cg-ay/J mice and mouse adipocytes. *Front Physiol*. 2021;12:12. doi:10.3389/fphys.2021.745058
151. Kasperova BJ, Mraz M, Svoboda P, et al. Sodium-glucose cotransporter 2 inhibitors induce anti-inflammatory and anti-ferroptotic shift in epicardial adipose tissue of subjects with severe heart failure. *Cardiovasc Diabetol*. 2024;23(1):223. doi:10.1186/s12933-024-02298-9
152. Lee SA, Riella LV. Narrative review of immunomodulatory and anti-inflammatory effects of sodium-glucose cotransporter 2 inhibitors: unveiling novel therapeutic Frontiers. *Kidney Int Rep*. 2024;9(6):1601-1613. doi:10.1016/j.ekir.2024.02.1435
153. Popoviciu MS, Salmen T, Reurean-Pintilei D, Voiculescu V, Pantea Stoian A. SGLT-2i—A useful tool for Real-life metabolic and body weight control in type 2 diabetes mellitus patients. *Medicina (B Aires)*. 2025;61(3):548. doi:10.3390/medicina61030548
154. Wu Q, Zhang J, Zhang F, Li D. SGLT2 inhibitors as metabolic modulators: beyond glycemic control in type 2 diabetes. *Front Endocrinol (Lausanne)*. 2025;16:1601633. doi:10.3389/fendo.2025.1601633
155. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77(3):243-255. doi:10.1016/j.jacc.2020.11.008

How to cite this article: Heuboeck E, Bhogal CS, Mandl M. Heart matters: How glucose- and lipid-modulating drugs remodel epicardial adipose tissue accumulation, inflammatory patterns and browning. *Diabetes Obes Metab*. 2026;28(2):878-894. doi:10.1111/dom.70324