

Review Article

Depot-specific adipose tissue modulation by SGLT2 inhibitors and GLP1 agonists mediates their cardioprotective effects in metabolic disease

Nour-Mounira Z. Bakkar¹,  Ibrahim AlZaim^{1,2} and  Ahmed F. El-Yazbi^{1,3,4}

¹Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; ²Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; ³Department of Pharmacology and Toxicology, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt; ⁴Faculty of Pharmacy, Alalamein International University, Alamein, Egypt

Correspondence: Ahmed El-Yazbi (ahmed.fawzy.aly@alexu.edu.eg)

Sodium-glucose transporter-2 inhibitors (SGLT-2i) and glucagon-like peptide 1 (GLP-1) receptor agonists are newer antidiabetic drug classes, which were recently shown to decrease cardiovascular (CV) morbidity and mortality in diabetic patients. CV benefits of these drugs could not be directly attributed to their blood glucose lowering capacity possibly implicating a pleotropic effect as a mediator of their impact on cardiovascular disease (CVD). Particularly, preclinical and clinical studies indicate that SGLT-2i(s) and GLP-1 receptor agonists are capable of differentially modulating distinct adipose pools reducing the accumulation of fat in some depots, promoting the healthy expansion of others, and/or enhancing their browning, leading to the suppression of the metabolically induced inflammatory processes. These changes are accompanied with improvements in markers of cardiac structure and injury, coronary and vascular endothelial healing and function, vascular remodeling, as well as reduction of atherogenesis. Here, through a summary of the available evidence, we bring forth our view that the observed CV benefit in response to SGLT-2i or GLP-1 agonists therapy might be driven by their ameliorative impact on adipose tissue inflammation.

Cardiovascular protection and antidiabetic drugs

One of the main challenges in the treatment of diabetic patients is the management of the associated cardiovascular diseases (CVDs), which represent the major cause of morbidity and mortality in this patient population. Indeed, the start point of CV complications in the course of metabolic disease seems to be obscure. Current evidence links the initiation of pathological processes culminating in cardiometabolic disease to pre-diabetes and its associated adipose tissue inflammation [1]. Relatedly, studies have shown that tight glycemic control per se is insufficient to reverse the CV derangements associated with diabetes [2]. This has motivated studies on drugs with pleotropic effects beyond glucose lowering. To this end, drugs such as metformin and pioglitazone have been tested for their anti-inflammatory effects [3]. Additionally, the CV safety of some of the approved drugs for diabetes management has been the concern of several clinical trials. In several landmark trials, sodium-glucose transporter-2 (SGLT-2) inhibitors (SGLT-2i) and glucagon-like peptide 1 (GLP-1) receptor agonists were not only shown to be safe but also appeared to be endowed with CV benefits beyond their glucose-lowering capacity [4–6], with benefits even in nondiabetic patients [7,8], triggering extensive interest in the potential mechanism of action [9–12].

The mechanism of action by which SGLT-2i and GLP-1 receptor agonists achieve their glucose-lowering effects is different. Particularly, the former promotes glucosuria by inhibiting active glucose reuptake along the renal proximal convoluted tubules, while the latter acts on GLP-1 receptors of pancreatic β -cells to stimulate insulin secretion and of α -cells to inhibit glucagon secretion. However, recent evidences support

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their combined use based on their complementary effects, tolerability, and CV benefit [13,14]. Researchers have inferred the presence of extra-glycemic effects of SGLT-2i from the fact that CV protection was achieved independent of glycated hemoglobin (HbA1c) levels [4,15]. Particularly, clinical trials indicated that CV benefits preceded normalization of HbA1c levels in diabetic individuals. Nonetheless, positive CV outcomes were evident in nondiabetic subjects with heart failure and coronary artery disease (CAD) [7,16] and were driven by changes in fat metabolism [17]. Indeed, a systematic review and meta-analysis of major cardiovascular outcomes trials confirms that cardiorenal benefits derived from SGLT-2i and GLP-1 receptor agonists are independent of their glycemic effects [18].

Both drug classes have been shown to exhibit desirable effects on adipose tissue depots implicated in CVDs [19–24], namely epicardial-, perivascular-, epididymal-, and inguinal- (ECAT, PVAT, EDAT, and IAT, respectively) as well as perirenal adipose tissue (PRAT). In fact, such propensity for the previously mentioned adipose tissues to be implicated in CVDs has been shown to be related to lower adipogenesis and differentiation capacity [25,26] as well as higher insulin resistance—as compared with subcutaneous adipose tissues (SAT)—under pathological conditions [27,28]. These characteristic are shown to promote hypoxia, a condition which triggers anaerobic fuel production mechanisms and promotes inflammation [17,24]. In previous studies on human subjects and animal models, we and others have pointed out that possible paracrine spillage of proinflammatory mediators from inflamed adipose depots to neighboring effector organs can trigger pathological consequences in the context of metabolic disorders and that selective amelioration of the localized inflammation is sufficient to reverse these detrimental changes [3,29–33].

In this review, we summarize clinical and preclinical evidence of thoracic and visceral adipose modulation by SGLT-2i(s) and GLP-1 receptor agonists culminating in cardiovascular benefit. We focus on ECAT, PVAT, and PRAT as direct, regional contributors to organ-specific diseases of the cardiovascular system. We also describe changes in abdominal adipose tissues systemically associated with cardiovascular disease, i.e., EDAT and IAT. Herein, we provide a separation between the differential, depot-specific effects of SGLT-2i(s) and GLP-1 receptor agonists, which might be related to the different characteristics of the adipose tissues and/or their expression of the respective effectors in health and disease, i.e., SGLT-2 and GLP-1 receptors.

We searched Google scholar and different search engines and databases for papers written in English on the cardioprotective effects of SGLT-2i(s) and GLP-1 receptor agonists mediated by changes in adipose tissues remodeling, metabolism, and inflammatory status. We mainly looked for articles combining both the adipose- and cardiovascular modulatory effects of SGLT-2i(s) and GLP-1 receptor agonists and studying both aspects in relation to one another, i.e., providing a link (correlation or association) between adipose tissue modulation and cardiovascular benefit. We used keywords and phrases like ‘effect of SGLT-2 inhibitors/GLP-1 receptor agonists on adipose tissue and cardiovascular function’ and ‘cardioprotective effect of adipose tissue modulation by SGLT-2 inhibitors/GLP-1 receptor agonists’. We also looked for similar research and mechanistic explanations among references of matching articles.

Heterogeneity of adipose depots imparts adipose tissue-specific characteristics

Adipose depots can be broadly classified into: thoracic, visceral, and subcutaneous. In fact, adipose tissues are not created equally as they are distinguished by their composition of mature and immature adipocytes, i.e. progenitor cells, also known as stromal vascular preadipocytes [28,34,35]. Mature adipocytes can be classified as white, brown, or brite (also known as beige), whereas preadipocytes and progenitor cells differ in their ability to proliferate and/or differentiate into mature adipocytes. The latter dictates the rates of hypertrophy and hyperplasia of the corresponding adipose pads in response to different physiological and pathological stimuli [34]. White adipocytes are known to be unilocular in nature, made up of a single large lipid droplet, and possess few mitochondria, while brown fat cells are multilocular and have abundant mitochondria. In fact, brown adipocytes acquire their color from the ample expression of uncoupling protein (UCP) 1, which uncouples the electron transport chain from adenosine triphosphate (ATP) production [36].

Alternatively, adipose tissues are disparate in their metabolic activity as well as their susceptibility to hypoxia which is thought to be dependent on their vascularization and the ability of their respective peri-adipose vessels to undergo angiogenesis [34,37]. Moreover, adipose pads vary in their expression levels of different metabolically involved proteins, like SGLT-2 and GLP-1 receptors, and how these are altered in disease conditions. The latter renders them differentially impacted by- and responsive to treatments.

Cardiac adipose tissues: the ECAT

Cardiac adipose tissue comprises different depots including the pericardial- and the epicardial adipose tissue (ECAT) classified by their location. Despite their close proximity, pericardial and ECAT are essentially distinct. ECAT is located between the cardiac muscle (the myocardium) and the pericardium and is perfused by branches of coronary arteries [38]. It is mainly composed of small, unilocular white adipocytes with the capacity to undergo browning under the effect of various stimuli. Indeed, human ECAT has been shown to express more UCP1 than most fat pads, which is thought to be protective to the myocardium against hypothermia [39]. ECAT is composed of more preadipocytes—or stromal vascular cells—than mature adipocytes [40].

Physiologically, ECAT functions as a thermoregulator and a lipid reservoir for myocardial energy [41]. This is particularly important in an adipose depot which heavily relies on free fatty acid oxidation for energy production [42]. The latter prevents excessive fat accumulation in ECAT [40]. Consistently, ECAT resembles visceral adipose tissues (VAT) in possessing lower insulin-induced glucose uptake than SATs [43]. In fact, fatty acid oxidation consumes more oxygen than glucose oxidation required to produce an equivalent amount of energy [44,45], which makes ECAT especially prone to hypoxia in the situation of insulin resistance and subsequent tissue expansion [46].

Additionally, ECAT preserves autonomic ganglia and nervous tissues and modulates coronary artery dynamics [41]. Thus, it is not surprising that changes in ECAT morphology, phenotype, and secretory profile have been shown to be associated with various cardiac diseases including heart failure, myocardial infarction, atrial fibrillation, and CAD [47–49] (Table 1). Particularly, ECAT volume and thickness have been associated with the previously mentioned cardiovascular abnormalities, whereby paracrine and endocrine signaling of adipocytokines derived from ECAT promotes deleterious effects on cardiac structure and function [50,51]. Interestingly, human ECAT was shown to express SGLT-2 as well as GLP-1 receptors, which renders it a therapeutic target in metabolic diseases [52–54].

Perivascular adipose tissue

Different vascular beds are surrounded with adipose tissues which not only exert a passive, barrier function but also perform paracrine signaling roles on to their neighboring vessels. Indeed, PVAT is actively involved in vascular dynamics, carrying out physiologically essential anticontractile and vasodilatory activities and secreting various mediators into the extracellular matrix affecting vascular smooth muscle- and endothelial cells [102–104]. PVAT include coronary- surrounding blood vessels of the heart-, thoracic-, and abdominal adipose pads.

PVAT comprises beige adipocytes, which share characteristics of white and brown adipocytes. Compared to subcutaneous adipocytes, perivascular adipocytes were shown to possess lower adipogenic differentiation capacity [105]. Alterations of PVAT secretory profile were shown to contribute to vascular diseases like CAD, pre-diabetic and Type 2 diabetic (T2D) vascular dysfunction, as well as atherosclerosis [106] (Table 1). Indeed, local inflammation and hypoxia of PVAT were shown to be associated with loss of its anticontractile function in obese subjects [81,80], whereby combating PVAT inflammation restores anticontractile properties independent of body weight [107]. Interestingly, it was shown that human pericoronary adipose fat overexpresses SGLT-2 in prediabetes with acute myocardial infarction [108]. Such an overexpression was shown to respond to antidiabetic treatment with pleiotropic anti-inflammatory effects, like metformin [108].

Visceral versus subcutaneous adipose tissues

Visceral adipose tissues exist in intra-abdominal cavities (i.e. omental and mesenteric) and provide protection for abdominal organs like the gonads (i.e., EDAT) and the kidneys (i.e., PRAT or retroperitoneal fat). Contrary to SATs, which are described to have a benign impact on cardiovascular, cardioautonomic, and/or cardiorenal function, visceral adipose tissues are associated with cardiometabolic disease states [109,110] (Table 1).

The limited capacity of visceral adipose tissues to expand is hypothesized to be at the origin of metabolic disorders [111]. Such a limitation is attributed, at least in part, to collagen deposition from the extracellular matrix, whereby increased pressure on hypertrophying adipose tissues is thought to induce chemokine secretion and subsequent macrophage infiltration which is disruptive of CV function [112,113]. In fact, early, adaptive responses to high calorie intake involve hypoxia-driven collagenase breakdown supporting extracellular matrix elasticity and healthy accommodation of fat with increased fatty acid uptake and synthesis [114–116]. Conversely, chronic hyperinsulinemia is described as an instigator of extracellular matrix deposition precipitating in unhealthy, fibrotic remodeling and subsequent dysfunctional adipocyte expandability [112,117]. Hence, drugs with the ability to reduce hyperinsulinemia by promoting insulin sensitivity and those with matrix metalloprotease activity are expected to promote extracellular matrix plasticity supporting healthy hypertrophy of adipose tissues [111].

Table 1 Role of epicardial, perivascular, and visceral adipose tissues in cardiovascular disease development and progression

Adipose depot	Changes	Mechanisms of cardiovascular dysfunction
ECAT [55,56]	Increased volume	Changes in cardiac electrophysiology [57], atrial fibrillation [58,59]
	Increased release of proinflammatory cytokines [60]	Coronary artery endothelial cell dysfunction [60]
	Increased thickness and altered miRNA expression [61–63]	Coronary heart disease [61] and coronary atherosclerosis [62]
	Changes in secretory profile [64–66]	Cardiomyocyte dysfunction and changes in cardiomyocyte metabolism (impairs β -oxidation) [64]
	Secretion of adipo-fibrokinase (Activin A, a member of TGF- β superfamily) [65,67,68]	Insulin resistance and reduced contractility of cardiomyocytes [65,66,69]
	Aberrant extracellular matrix remodeling [70]	Atrial myocardial fibrosis possibly precipitating atrial fibrillation [67]
	Increased thickness [58, 71, 72]	Severe ischemic cardiomyopathy [70]
	Chronic adrenergic stimulation and elevated lipolytic activity precipitating ECAT inflammation [73]	Reduced cardiopulmonary performance [71]
	Impaired prostaglandin E2 regulation [74]	Altered myocardial redox state [75]
	Increased resistin content [76]	Cardiac remodeling [73]
PVAT [78,79]	Suppressed release of adiponectin [77]	Maladaptive cardiovascular remodeling in overweight subjects [74]
	Releases adipokines [77]	Advanced coronary atherosclerosis and history of myocardial infarction [76]
	Reduction in omentin 1	Increased severity and progression of coronary artery disease [72]
	Inflammation [80] and hypoxia [81]	Atherogenic changes in myocytes and endothelial cells [77]
	Hypertrophy (increased abdominal PVAT adipocyte size)	Impairment of insulin-induced uptake by cardiomyocytes [68]
	Changes in T cell and macrophage subtypes [84]	Loss of anticontractile properties [81,80,82]
	Chemokine-induced inflammation [85]	Cardiac autonomic neuropathy [33,83]
	Secretion of TNF- α [82]	Hypertension [84]
	Source of oxidized LDL (pericoronary adipose tissues) [88]	Vascular oxidative stress and endothelial dysfunction [3,85,86]
	Elevated leptin production [86] and oxidative stress [89]	Reduced endothelial nitric oxide bioavailability [87]
Visceral adipose tissues [92]	Increased extracellular matrix protein deposition, e.g., osteopontin in epididymal fat [93]	Formation of human coronary plaque [88]
	Secretion of exosomes [94]	Vascular resistance to the vasodilatory effects of leptin [90]
	Increased volume [96]	Vascular inflammation and blood clotting [91]
	Releases proinflammatory adipokines like leptin [97] and/or resistin [92]	Increased myocardial interstitial fibrosis and dysfunction in aging [93]
	Increased mass [98]	Increased myocardial oxidative stress and extracellular matrix deposition via mineralocorticoid receptor activation, reactive oxygen species production, release of profibrotic proteins, and collagen production in myofibroblasts [95]
	Secretion of cytokines like TGF- β	Atherogenesis, regulating macrophage polarization, and foam cell formation [94]
	Increased thickness [101]	Higher aortic inflammation [96]
		Increased vascular calcification [99]
		Precipitates endothelial [100] and vascular dysfunction by decreasing endothelial nitric oxide synthase uncoupling, increasing nitric oxide production, as well as increasing the release of proinflammatory cytokines, cell adhesion molecules (like ICAM and VCAM), and vasoconstrictors (like endothelin and PAI-1) [92]
		Exacerbates atherogenesis and plaque rupture, restenosis, and hypertension by acting on vascular smooth muscle cells and altering macrophage infiltration and profile [92]
	Increased circulating proteins like IL-16, IL-1 receptor agonist, tumor necrosis factor and its receptor, growth factors like vascular endothelial growth factor-A, and fibroblast growth factor 23, matrix metalloproteinase 7, selectin, myoglobin, and leptin associated with CVDs [98]	
	Increased leptin-induced adiponectin release by adrenocortical cells promoting mineralocorticoid receptor-induced cardiac fibrosis and vascular endothelial dysfunction (reduced endothelial dependent vasodilation) [97]	
	Increased resting heart rate [101]	

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In keeping with their cardioprotective characteristics, SATs were found to have larger adipocytes than VATs, albeit lower inflammatory infiltration by M1 phenotype macrophages and higher expression of adiponectin [118]. On the other hand, human SATs possess higher adipogenesis and adipose differentiation capacity [119] supporting hyperplasia, as well as higher browning ability [120].

SGLT-2i and adipose modulation

ECAT and SGLT-2i

A pilot study in T2D patients reported a decrease in ECAT volume with luseogliflozin, which significantly correlated with a reduction in systemic microinflammation, demonstrated as lower C-reactive protein levels [121]. Of note, a drop in body weight was observed in the recruited subjects, although they remained overweight and no change in visceral fat area was evident [121]. In T2D patients with CAD, a similar observation was made with dapagliflozin treatment, whereby a decrease in ECAT volume was accompanied with a significant reduction in plasminogen activator inhibitor-1 and was significantly associated with a decrease in TNF- α [122].

On the other hand, treatment of T2D patients with canagliflozin significantly reduced ECAT thickness as early as three months, even before a reduction in glycated hemoglobin was observed [123]. Moreover, at six months of treatment, despite a significant decrease in HbA1C, no correlation between changes in HbA1C and ECAT thickness was present [123]. It is worth noting that such a reduction occurred in the absence of changes in visceral or subcutaneous adipose tissues thickness. Consistently, it was shown that the drop in ECAT thickness in response to SGLT-2 inhibition is unrelated to weight loss [124]. In obese T2D patients, addition of dapagliflozin to metformin therapy decreased ECAT thickness at three months, before changes in body weight occurred. After six months of treatment, while weight loss was significant, changes in ECAT thickness and body weight did not correlate [124].

An *ex vivo* study revealed that ECAT from patients undergoing cardiac surgery expressed SGLT-2, suggesting a direct effect for SGLT-2i(s) on ECAT [52]. Treatment of epicardial fat explants with dapagliflozin increased glucose uptake in samples from subjects with or without insulin resistance, by increasing glucose transporter 4 (GLUT-4) expression, indicating increased insulin sensitivity (Figure 1). A similar study indicated that such an effect coincided with a decrease in oxygen consumption in ECAT, an event which is of particular significance in tissues prone to hypertrophic expansion and hypoxia [17]. Concomitantly, enhanced mitochondrial biogenesis in dapagliflozin-treated ECAT was demonstrated by an increased expression of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) [17].

In fact, it was proposed that the decrease in oxygen consumption might be related to either a shift in energy substrate from fatty acid to glucose and a subsequent increase in oxygen efficiency or an augmented proton leak associated with PGC-1 α -induced mitochondrial biogenesis. Interestingly, the latter provides an alternative inducible uncoupling mechanism—i.e., UCP2/3-dependent—with the capacity to dissipate excess energy in the form of heat [125] and possibly reduce ECAT volume (Figure 1). Importantly, treatment with dapagliflozin reduced secreted levels of L-lactate, a product of anaerobic glycolysis, which were shown to increase in ECAT, as opposed to SAT, and to be associated with CAD [17]. Results confirm that L-lactate was not alternatively converted into glycerol and used in lipid storage. It is worth noting that such observations were made in samples from heart failure, CAD, arterial hypertension, or T2D patients [17,52].

Interestingly, CV benefit of dapagliflozin was linked to improved glucose uptake. Dapagliflozin reduced the secretion of ECAT adipokines, CXCL8, CCL2 (also known as monocyte chemoattractant protein 1, MCP1), and CCL5 exclusively in biopsies with insulin resistance (Figure 1) [52]. Of note, CCL2 in ECAT secretosomes, which was shown to be higher in patients with CAD, was only reduced in samples with increased glucose uptake in response to dapagliflozin, revealing a possible role for increased oxygen efficiency in the reduction of hypoxia-driven inflammation. Functionally, under paracrine effect, secretosomes from ECAT samples with improved glucose uptake conferred an increased wound healing capacity on human coronary endothelial cells [52].

Conversely, while dapagliflozin did not increase glucose uptake in adipogenesis-induced ECAT stromal vascular cells, it did enhance their differentiation. Alternatively, adipogenesis-induced stromal vascular cells treated with dapagliflozin showed reduced acidosis. Opposite effects were observed in SAT (vs. ECAT) with regards to adipogenesis and differentiation of stromal vascular cells [52].

Perhaps the most intriguing effect of ECAT modulation by SGLT-2i is its capacity to alter cardiac electrophysiology, specifically markers of atrial fibrillation like those derived from P-wave duration of electrocardiography [126]. In an ad hoc study of the previously described study population, treatment with dapagliflozin for 6 months was shown to significantly reduce body weight with respect to conventional treatment. Interestingly, despite the absence of significant inter- and intra-group differences and changes in glycemic markers including insulin resistance, a significant

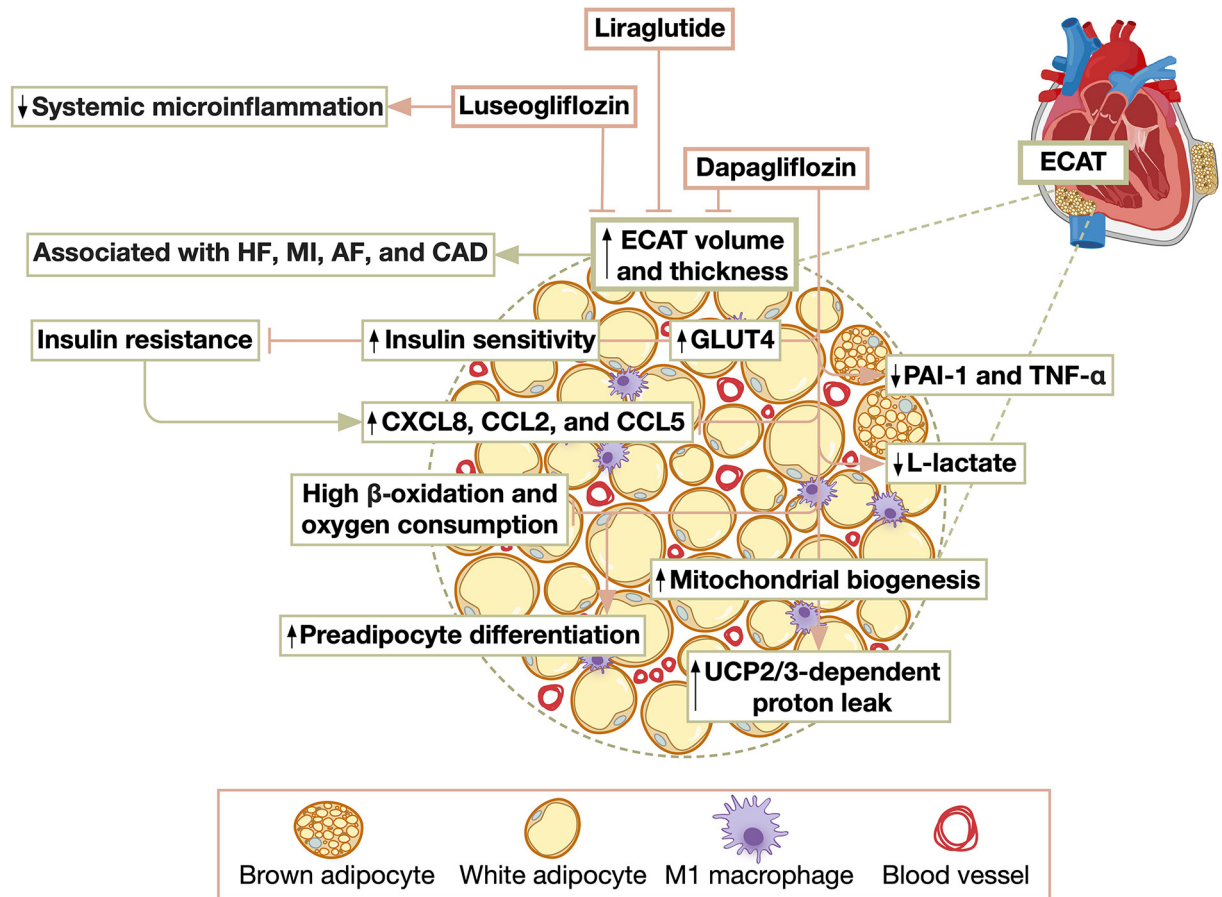


Figure 1. Effects of sodium-glucose transporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) on epicardial adipose tissue (ECAT)

Increased ECAT thickness and volume is associated with heart failure (HF), myocardial infarction (MI), atrial fibrillation (AF), and coronary artery disease (CAD). SGLT-2i and GLP-1RA decrease ECAT thickness and volume. SGLT-2i were found to increase glucose uptake via glucose transporter 4 (GLUT4) in ECAT, increasing oxygen efficiency, decreasing the secretion of ECAT adipokines (CXCL8, CCL2, CCL5), and enhancing pre-adipocyte differentiation. Desirable shifts in energy substrate, increase in mitochondrial biogenesis, and energy dissipation were shown to underlie amelioration of ECAT function with SGLT-2i. Abbreviations: PAI, plasminogen activator inhibitor; TNF- α , tumor necrosis factor- α ; UCP, uncoupling protein.

reduction in ECAT volume and serum TNF- α was observed in the dapagliflozin-treated group [126]. Concomitantly, a significant difference in changes in maximum P-wave duration, dispersion (measured as the difference between maximum and minimum P-wave duration), and variation (defined as the standard deviation of P-wave duration) were reported between dapagliflozin- and conventionally treated T2D patients with CAD, with these parameters decreasing in response to dapagliflozin treatment only [126]. Changes in P-wave dispersion significantly correlated with changes of both ECAT volume and serum TNF- α concentration. However, the study by Sato et al. indicates that ECAT is directly involved in arrhythmogenesis as ECAT volume, rather than TNF- α , was independently associated with P-wave dispersion [126].

SGLT-2i, PVAT, and vascular disease

Inflammation of PVAT has been linked to cardiovascular outcomes in pre-diabetes and T2D through vascular endothelial dysfunction and cardiac autonomic neuropathy [3,33,83, 127, 128]. Treatment with ipragliflozin was shown to enhance ‘healthy’ expansion of abdominal—but not thoracic—PVAT in mice fed a western diet [129]. Adipocyte size in abdominal PVAT of western diet-fed mice further increased and Akt phosphorylation was recovered under the effect of SGLT-2i [129]. The latter was associated with decreased expression of proinflammatory- (*ccl2* and *emr1*) and

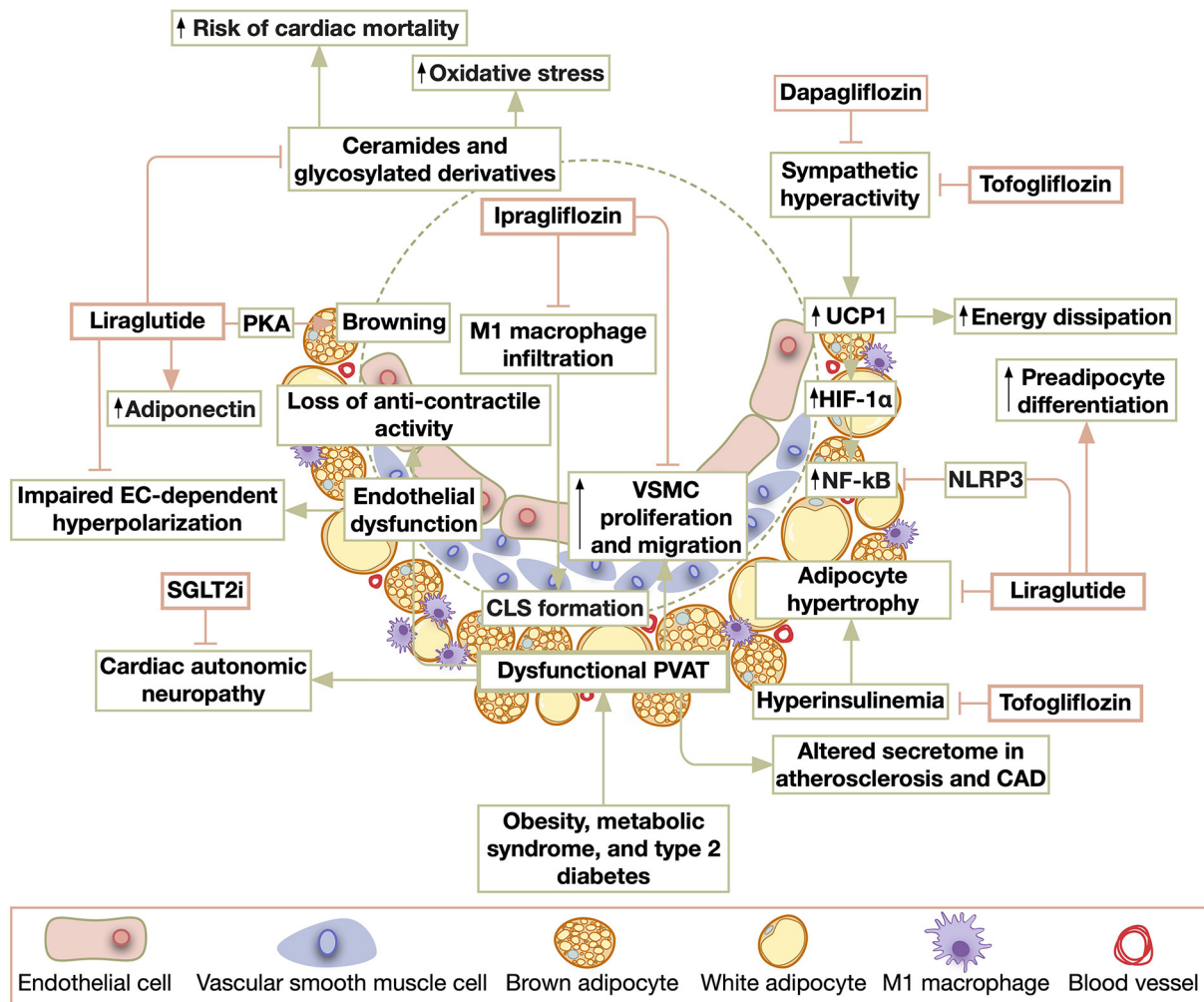


Figure 2. Effects of SGLT-2 inhibitors and GLP-1R agonists on PVAT

Dysfunctional PVAT secretome aggravates vascular diseases like atherosclerosis and CAD. Alleviation of PVAT dysfunction via SGLT-2 inhibition and/or GLP-1R activation is associated with improved vascular endothelial and smooth muscle cell properties. SGLT-2i and GLP-1RA promote healthy PVAT remodeling, which inhibits localized proinflammatory signaling pathways. Reversal of cardiac autonomic neuropathy with SGLT-2i correlates with improved adipose tissue insulin sensitivity possibly explaining the amelioration of adipose tissue function. Abbreviations: CLS, crown-like structure; EC, endothelial cell; HIF- α , hypoxia-inducible factor- α ; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; PKA, protein kinase A; VSMC, vascular smooth muscle cell.

profibrotic (*coll1a1*, *coll1a2*, and *fn1*) genes as well as lower macrophage infiltration and crown-like structure formation. In line with these changes, ipragliflozin treatment of western diet-fed mice reduced adipocyte apoptosis in abdominal PVAT [129]. PVAT isolated from ipragliflozin-treated mice had lower expression of vascular smooth muscle cells (VSMCs) proliferation and migration-related genes like visfatin, angiotensin-like protein 1, and fatty acid binding protein 4 (FABP4) and secreted less leptin into the cellular matrix. The latter correlates with lower PI3K-mediated migration of VSMCs incubated with cellular matrix of PVAT from ipragliflozin-treated mice (Figure 2) [129].

Studies by Mori et al. indicate that modulation of pathogenic PVAT mediates the protective effect of SGLT-2i(s) against injury-induced vascular remodeling in mouse models of atherosclerosis [129,130]. Particularly, in apolipoprotein E-deficient mice, implantation of EDAT isolated from ipragliflozin-treated mice on western diet around femoral arteries reduced neointimal hyperplasia and synthetic switch following cuff-injury [129]. On the other hand, unilateral excision of PVAT or luseogliflozin treatment of apolipoprotein E knockout mice on high-fat diet attenuated wire-induced increase in intima-to-media thickness, in a mutually exclusive manner implicating the mediating role of PVAT in the aforementioned effect of SGLT-2i [130]. Reduction of neointimal hyperplasia significantly correlated

with reduced PVAT gene expression of platelet-derived growth factor-B. Indeed, PVAT from luseogliflozin-treated mice had lower macrophages expressing platelet-derived growth factor-B [130]. This was concomitant with an increased adiponectin gene expression in PVAT of luseogliflozin-treated mice. It is worth noting the differential effects of SGLT-2 inhibition on PVAT adipocyte size from mice on different diets, whereby the vascular ameliorative effects of ipragliflozin treatment were attributed to a healthy increase in adipocyte size in western diet-fed mice [129] while a decrease in adipocyte size was observed in high fat diet-fed mice treated with luseogliflozin [130].

One of the mechanisms by which SGLT-2i is presumed to abolish the driving force of visceral fat inflammation is by inhibition of sympathetic outflow. Indeed, under the effect of hyperinsulinemia and concomitant sympathetic hyperactivity, visceral adipose depots upregulate UCP1 in an attempt to dissipate excess energy in the form of heat [131]. However, increased UCP1 expression is particularly problematic in poorly vascularized adipose depots endowed with hypertrophic rather than hyperplastic expansion capacity, like PVAT [132]. This can be explained by the exaggerated oxygen consumption required for UCP1 activity which increases the propensity of such adipocytes for hypoxia-induced inflammatory processes along the hypoxia-inducible factor α (HIF- α)-nuclear factor κ B (NF- κ B) axis [133].

A recent study revealed that the capacity of tofogliflozin to decrease resting heart rate, a marker of sympathovagal imbalance, correlates with a reduction in adipose-tissue specific insulin resistance and subsequent hyperinsulinemia in T2D patients (Figure 2) [134]. In fact, a study revealed a direct, acute central inhibition of sympathetic outflow in healthy mice treated with dapagliflozin [135]. SGLT-2 was found to be expressed in the brainstem, particularly in the nucleus of the solitary tract. Dapagliflozin treatment was shown to increase c-Fos, a marker of neuronal activation, expression in autonomic regions like the paraventricular nucleus, reticular nucleus, and locus coeruleus of the brainstem and precisely in regions expressing SGLT-2 [135]. Such changes brought about decreased blood pressure in healthy mice treated with dapagliflozin.

How sympathetic inhibition, parasympathetic activation, and subsequent sympathovagal balance normalization by SGLT-2i act at the level of adipose tissue remains unclear and warrants further investigation. This is particularly relevant in light of the evidence on the proinflammatory and anti-inflammatory effects of sympathetic and parasympathetic activation, respectively [136], specifically at the level of PVAT as shown in preliminary studies [137]. While one study indicates increased intra-adipose sympathetic innervation of SAT to be responsible for the antiobesogenic effect of canagliflozin [138], another shows an acute decrease in sympathetic activity associated with reduced UCP1 expression in brown adipose tissues in response to dapagliflozin [139]. The latter needs to be addressed in different adipose depots on chronic time points.

Indeed, our previous work has shown that progression from pre-diabetes to Type 2 diabetes is associated with worsening of cardiac autonomic control in parallel with a change in the status of inflammation from being localized in PVAT to being systemic and central, involving suppression of brainstem autophagic flux possibly triggering apoptosis [33]. Interestingly, SGLT-2i(s), like canagliflozin and dapagliflozin, were found to suppress central inflammation and ameliorate apoptosis in models of the metabolic syndrome [140,141]. This comes in line with accumulating evidence on the ameliorative effect of SGLT-2i(s) on cardiac autonomic neuropathy [142].

Epididymal-, inguinal-, and perirenal adipose tissue and SGLT-2i

EDAT, like PVAT, was shown to undergo healthy expansion under the effect of SGLT-2 inhibition. In mice on western diet, increased EDAT weight-to-body weight upon treatment with ipragliflozin was associated with a decrease in its release of atherosclerosis-promoting proteins like high motility group box 1 (HMGB1) and FABP4 into the cellular matrix (Figure 3) [129]. Consistently, cellular matrix of EDAT from ipragliflozin-treated mice was shown to promote lower MCP-1-mediated monocyte migration compared with western diet-fed mice [129].

Under the effect of ipragliflozin in high fat diet-fed mice, EDAT expansion was accompanied with decreased M1 to M2 ratio of macrophages with proinflammatory and anti-inflammatory characteristics, respectively [143]. Interestingly, healthy expansion of EDAT was attributed to decreased M1-like macrophages and their related gene expression (*Il-1 β* and *Tnf- α*) rather than an increase in M2-like macrophages and their associated genes [143]. Mechanistically, it was demonstrated that ipragliflozin-induced increase in ketone bodies possibly underlies favorable adipose remodeling through a reduction in IL-15-mediated suppression of lipogenic genes. Indeed, IL-15 release from M1 macrophages in the stromal vascular fraction of EDAT was decreased by ipragliflozin (Figure 3) [143]. Further, treatment with ipragliflozin was shown to reduce EDAT production of ceramides and sphingomyelin [143], which could possibly explain its presumed cardiovascular protective effect in diseases like hypertension, atherosclerosis, and heart failure [144].

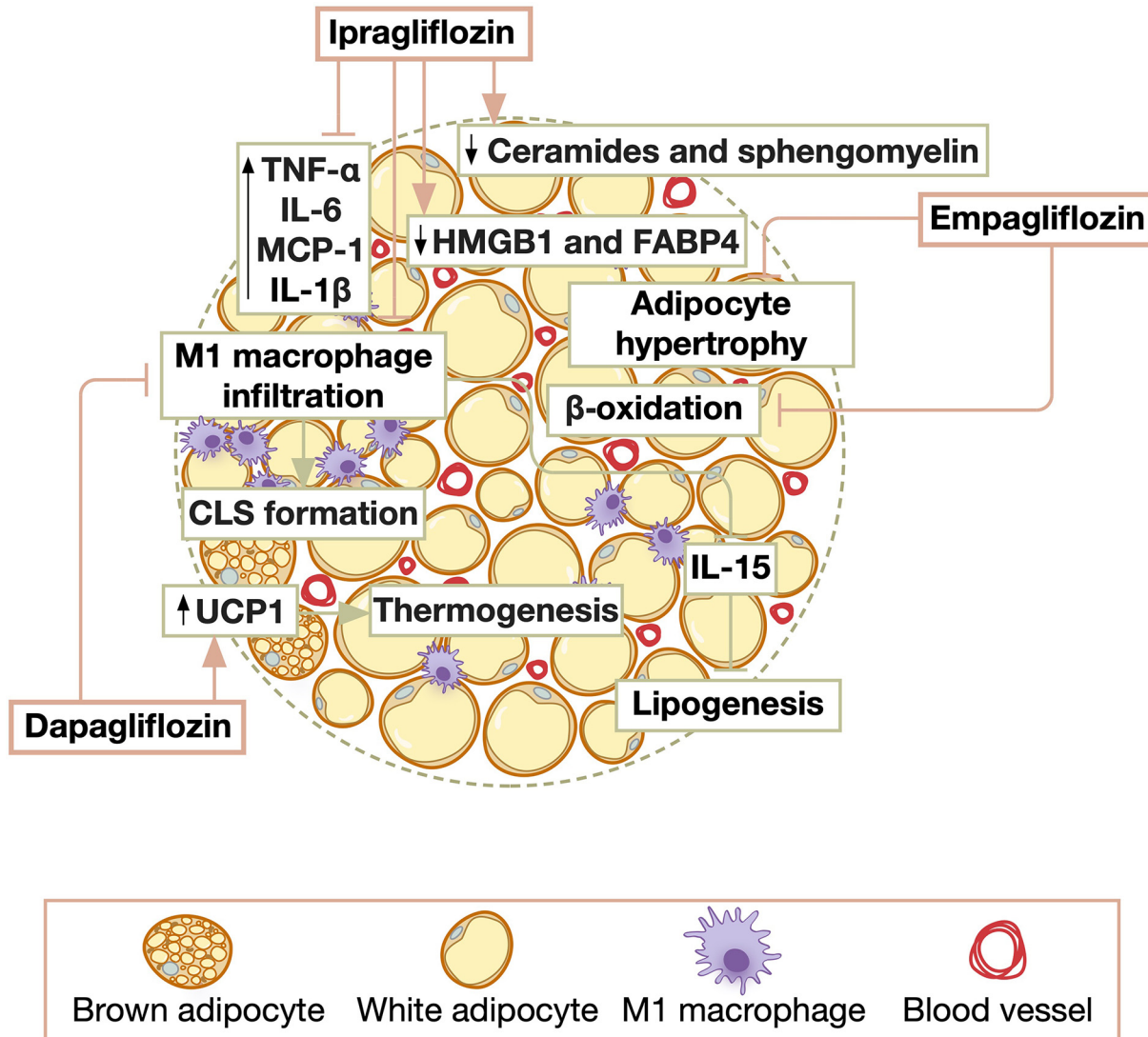


Figure 3. Effect of SGLT-2is on EDAT

SGLT-2 inhibition suppresses proinflammatory processes in EDAT by inhibiting cytokines release as well as macrophage infiltration. SGLT-2is promote EDAT thermogenesis via uncoupling protein 1 (UCP1). SGLT-2 inhibition in EDAT is associated with lower expression of atherosclerosis-promoting proteins like high motility group box 1 (HMGB-1), fatty acid binding protein 4 (FABP4), ceramides, and sphingomyelin. Abbreviations: IL, interleukin; MCP-1, monocyte chemoattractant protein 1; NF- κ B, nuclear factor- κ B; TNF- α , tumor necrosis factor- α .

Alternatively, in diet-induced obese mice treated with empagliflozin, modulation of macrophage polarization, favoring M2 over M1 phenotype, was associated with browning of epididymal and inguinal adipose depots as well as reduced insulin resistance and systemic inflammation [145]. Consistently, dapagliflozin treatment of differentiated human visceral adipocytes was shown to be associated with increased UCP1 expression [131].

In a rat model of prediabetes with metabolic syndrome (SHRcp), empagliflozin produced a drop in body weight mainly driven by decrease in subcutaneous fat weight [146]. Whereas both epididymal and subcutaneous fat from empagliflozin-treated rats demonstrated lower average adipocyte size as well as a lower and higher proportion of large and small adipocytes, respectively, only epididymal fat exhibited significantly lower levels of lipid oxidation [146]. Interestingly, these changes were associated with improved parameters of cardiac injury demonstrated by reduced cardiac hypertrophy, fibrosis, oxidative stress, and interstitial macrophage infiltration. However, no difference in cardiac autonomic function was observed with amelioration of epididymal fat metabolic state [146]. It is worth

noting the absence of a healthy group of rats, necessary for the identification of pathological deviations from normal levels in pre-diabetic rats.

Despite the demonstrated direct impact of SGLT-2 inhibition on visceral adipose tissues, a study of the vasorelaxant activity of arteries from human visceral adipose depots reflects a bidirectional ameliorative effect for canagliflozin in the relationship between visceral adipose tissue- and vascular dysfunction in obese individuals. Restoration of vasodilation derived from treatment with canagliflozin was shown to be related to inhibition of arterial Na^+/H^+ exchanger [147]. While the study concluded a possible SGLT-2i-related relief of visceral adipose tissue burden on the vasculature, it cannot preclude the opposite conclusion whereby the observed improvement in vasodilation, as a direct consequence of SGLT-2 inhibition in visceral adipose tissues arteries, improves adipose tissue function in obese individuals by reoxygenation of the hypoxic adipose depot secondary to increased blood supply [147].

Interestingly, a recent study suggests that ipragliflozin ameliorates signs of diabetic nephropathy in a mouse model of T2D by decreasing PRAT spillage of leptin and its paracrine signaling to the kidney, without a change in body weight [148]. The former was shown to be associated with enhanced insulin sensitivity and healthy remodeling of PRAT with a reduced burden of inflammation, fibrosis, and apoptosis [148]. Treatment with ipragliflozin improved proteinuria and suppressed glomerular hypertrophy, concomitant with a decrease in fatty acid transport and synthesis gene expression in the kidney [148]. As renal vein serum leptin concentration correlated with urinary albumin excretion *in vivo*, glomerular endothelial cells incubated with PRAT conditioned medium from high fat diet-fed mice exhibited elevated leptin-dependent cellular proliferation signaling [148]. Consistently, ipragliflozin treatment reduced p38 mitogen-activated protein kinase (MAPK) phosphorylation and proliferating cell nuclear antigen (PCNA) expression in glomerular endothelial cells.

GLP-1 receptor agonists and adipose modulation

GLP-1 agonists and thoracic adipose tissues

In obese, T2D patients with blood glucose levels controlled by metformin monotherapy ($\text{HbA1c} \leq 8\%$), addition of liraglutide reduced ECAT thickness (Figure 1) as well as indexed left ventricular mass as early as three months of treatment [149]. Significantly, ECAT thickness correlated with a drop in HbA1c which was not evident in the metformin group. It is worth mentioning, however, that baseline body weight was significantly higher in the group allocated to receive liraglutide add-on and was only reduced in this group, though no correlation between changes in body weight and ECAT thickness was evident [149]. In fact, percent reduction of ECAT established in T2D patients treated with liraglutide was shown to be the greatest when compared with other visceral and subcutaneous adipose beds [150]. Indeed, GLP-1 receptor was found to be expressed in ECAT from subjects with CAD and to be correlated with genes of β -oxidation, white-to-brown differentiation including UCP1, and adipogenesis [53].

Interestingly, the cardioprotective effect of liraglutide has also been attributed to thoracic adipose tissue metabolome reprogramming in obese individuals [151]. In obese, atherosclerotic patients, hypertrophy of intrathoracic adipose tissues was shown to correlate with elevated vascular oxidative stress [152]. Such an association was found to be mediated by endocrine spillage of ceramides, and their glycosylated derivatives, from thoracic fat-derived secretosomes [152]. Consistently, circulating ceramides correlated with systemic inflammation and increased risk of cardiac mortality [152]. Following a low-calorie diet, 1-year treatment with liraglutide was found to reduce circulating levels of ceramides implicated in cardiovascular dysfunction [151,152]. A similar suppression of plasma ceramide levels was also reported in T2D patients treated with liraglutide, but not with glimepiride, in combination with metformin [153].

GLP-1 agonists, PVAT, and endothelial function

Treatment with liraglutide was also shown to decrease peri-aortic fat in T2D patients [150]. The impact of PVAT dysfunction on vascular contractility and endothelium-dependent hyperpolarization has been previously demonstrated in models of metabolic syndrome [3,154]. A study by Han et al. further implicated PVAT in vascular dysfunction of the metabolic syndrome by showing that liraglutide treatment is capable of normalizing vascular structure/morphology as well as anticontractile and endothelium-dependent dilatory responses in a PVAT-dependent mechanism in obese rats (Figure 2) [155]. It shows that liraglutide enhanced thoracic PVAT browning and antioxidant defense through PKA-induced phosphorylation of AMPK- α and eNOS, a mechanism which is independent of cAMP. Improved vascular properties in light of PVAT modulation can possibly be attributed to paracrine signaling through increased adiponectin secretion [103,155]. Alternatively, a study in Zucker diabetic fatty rats revealed that liraglutide treatment is capable of reducing the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in PVAT via inhibition of NF- κ B (Figure 2) [156].

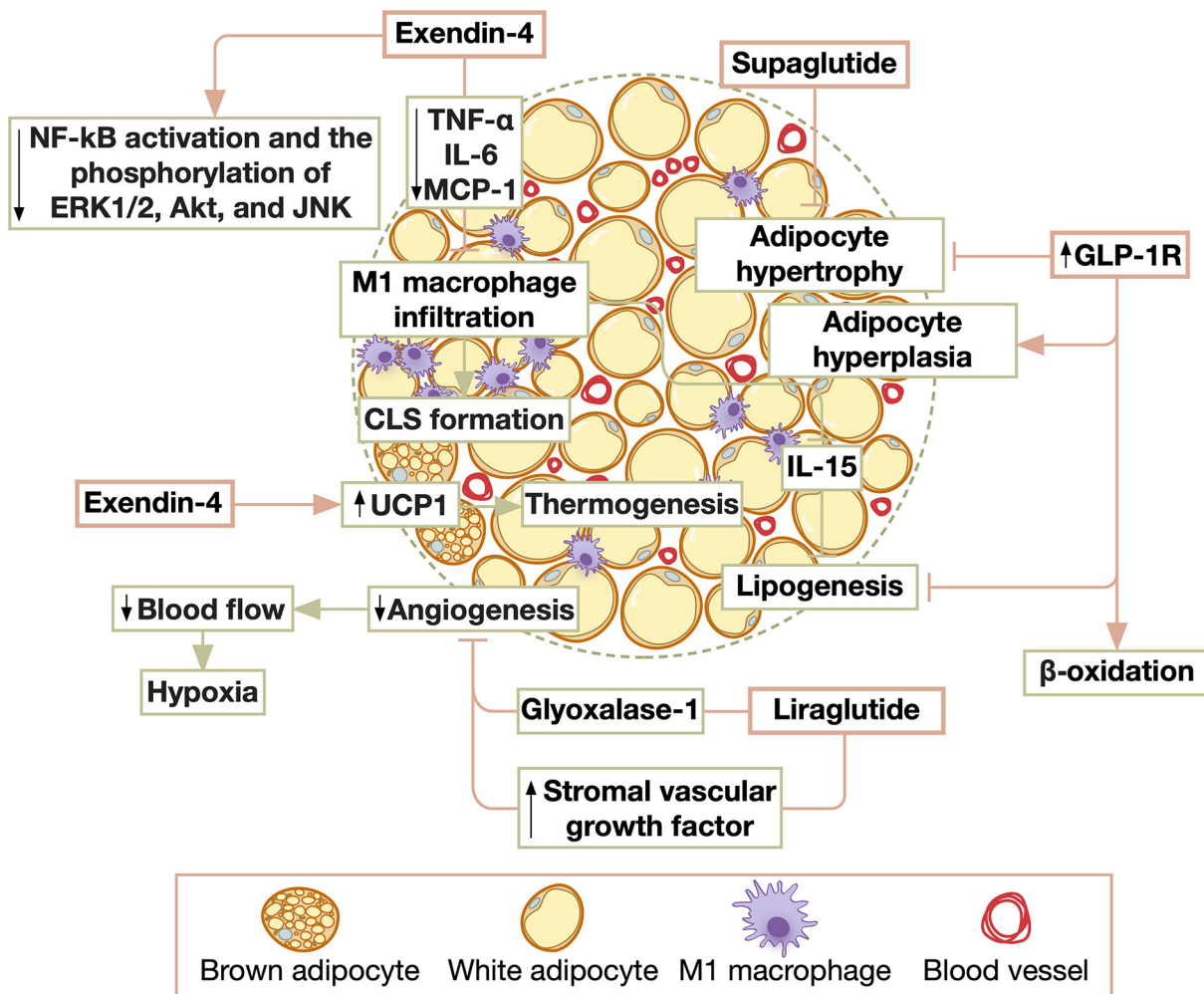


Figure 4. Effect of GLP-1RAs on EDAT

GLP-1RAs support the healthy expansion of EDAT by enhancing angiogenesis, a process which reduces hypertrophy-induced hypoxia. Additionally, GLP-1RA are associated with enhanced hyperplasia. Abbreviations: Akt, Protein kinase B; ERK, extracellular signal-regulated kinase; IL, interleukin; JNK, c-Jun N-terminal kinase; MCP-1, monocyte chemoattractant protein 1; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; UCP, uncoupling protein.

Interestingly, dipeptidyl peptidase-4 inhibitor, alogliptin, through a GLP-1-dependent mechanism, demonstrated a positive impact on endothelial relaxation mediated by reversing autophagy inhibition in PVAT of an obese rat model [157]. Indeed, induction of PVAT autophagy *ex vivo* did not occur except in the presence of GLP-1. Evidently, activation of autophagic flux was accompanied with anti-inflammatory effects demonstrated by increased adiponectin and decreased TNF-α expression in PVAT [157]. Like SGLT-2, receptors of GLP-1 were found to be expressed in hypothalamic and brainstem regions involved in autonomic control [158]. This may partly explain the association between GLP-1 agonists, PVAT modulation, and cardiovascular benefits. However, more research in this area is warranted.

GLP-1 agonism and EDAT, IAT, and PRAT

In an obese mouse model of diabetes (*ob/ob*), overexpression of GLP-1 by recombinant adenovirus was shown to bring about a drop in body weight associated with a reduction in percent fat mass [159]. Interestingly, while no change in SAT weight was observed secondary to GLP-1 overexpression, the latter produced a decrease in insulin resistance along with a marked reduction in perirenal, mesenteric, and epididymal fat mass [159]. Moreover, constitutional expression of GLP-1 reduced epididymal adipocytes size and increased their number (Figure 4). While the former was a result of reduced lipogenesis and increased fat oxidation [159], the latter suggests hyperplasia. Importantly, suppressed lipogenesis was not related to reduced food intake as pair-fed mice lacked a similar change [159]. In fact,

treatment of obese (*ob/ob*) mice with liraglutide was shown to reduce the expression of fatty acid synthase, a key enzyme in lipogenesis, in visceral adipose tissues [160].

GLP-1 treatment reduced proinflammatory signaling via decreased expression of NF- κ B and phosphorylation of ERK1/2 and JNK in epididymal fat of obese T2D mice [159] (Figure 4). Indeed, stromal vascular cells of epididymal fat from GLP-1-treated mice showed lower macrophage infiltration, particularly triple positive, F4/80+/CD11b+/CD11c+ cells, and reduced expression of markers of activated M1, proinflammatory macrophages (F4/80 and *Tlr4* genes) [159]. Additionally, EDAT from GLP-1-treated mice exhibited lower expression of proinflammatory cytokines like IL-6, TNF- α , and MCP-1 [159]. Peritoneal macrophages showed similar changes. In a different model of the metabolic syndrome, treatment of wild-type high-fat fed mice with exendin-4, a GLP-1 mimetic and receptor agonist, produced similar results, whereby EDAT macrophages isolated from these mice exhibited reduced gene expression of IL-6, TNF- α , and MCP-1 [159]. Consistently, *ex vivo* treatment of cultured EDAT macrophages from high-fat fed mice with exendin-4 yielded lower expression of the aforementioned proinflammatory cytokines.

Alternatively, *in vitro* experiments on 3T3-L1 adipocytes challenged with lipopolysaccharide (LPS) reveal direct, pleiotropic anti-inflammatory effects of GLP-1 receptor agonists, independent of glucose normalization and insulin sensitization. Indeed, pretreatment of 3T3-L1 with exendin-4 suppressed LPS-induced NF- κ B activation and reduced phosphorylation of ERK1/2 and Akt [159]. A study by Rodrigues et al. describes a possible mechanism for the above mentioned observations in preclinical models [161]. It shows that liraglutide is capable of up-regulating EDAT angiogenesis, increasing blood flow, and reducing hypoxia via a glyoxalase-1-dependent mechanism in a diabetic rat model (Figure 4) [161]. Glyoxalase-1, an enzyme responsible for breaking down toxic methylglyoxal and preventing its accumulation, was found to be down-regulated in visceral, but not subcutaneous, adipose tissues of diabetic obese subjects [161]. Importantly, it was demonstrated that the ability of liraglutide to induce periepididymal capillarization is supported by its induction of stromal vascular growth factors [161]. Such findings propose a role for GLP-1 receptor agonists in promoting healthy expandability of VAT mediated, at least in part, by methylglyoxal inhibition, which is expected to underlie its cardioprotective effect [162–165].

In high-fat fed obese mice, supaglutide reduced both epididymal and inguinal adipocyte size, but induced UCP1 expression exclusively in IAT, an event associated with improved whole body insulin sensitivity [166]. On the other hand, a different study reports a reduction in adipocyte hypertrophy associated with adipocyte-specific SIRT-1-dependent browning of EDAT in response to exendin-4 [167]. This is consistent with findings in differentiated human visceral adipocytes, whereby treatment with exendin-4 enhances UCP1 expression [131]. Interestingly, a recent study provides that liraglutide improves visceral adipocyte insulin sensitivity through management of hypertrophy-induced endoplasmic reticulum stress via regulation of autophagy also known as unfolded protein response [168].

Despite the scarcity of studies on the impact of GLP-1 receptor agonists on perirenal adipose depots and renovascular events, preclinical and clinical evidence indicate that liraglutide significantly reduces perirenal fat accumulation and suggests its association with improvement of renal vascular resistance and other markers of kidney function [150,169]. In fact, a study by Zhu et al. shows that treatment of high-fat fed obese mice with liraglutide induces browning of PRAT via a direct stimulation of the soluble guanylyl cyclase pathway, possibly explaining the reduction in PRAT adipocyte size [170]. In light of the recent study showing the cardiorenal protective effects of an exendin-based GLP-1 agonist, efpeglatide, further studies on the modulatory effect of this drug class on PRAT are warranted [171].

GLP-1 agonism and adipogenesis: Involvement of classical Wnt signaling

Several studies indicate direct, adipose tissue-specific effects for GLP-1/GLP-1 receptor signaling on adipogenesis [172,173]. Particularly, treatment of murine pre-adipocytes (3T3-L1) with liraglutide promotes their proliferation and differentiation and inhibits their apoptosis [172]. Such an increase in adipogenesis was shown to be evident irrespective of changes in body weight, as mice fed a high-fat diet and treated with liraglutide demonstrated a similar stimulation of adipogenesis despite weight loss [172].

It was demonstrated that GLP-1 receptor is a G-protein-coupled receptor as its activation with liraglutide was associated with elevated cyclic adenosine monophosphate (cAMP) and that its expression in 3T3-L1 cells is linked to PPAR- γ , a maker of adipocyte differentiation [172]. Importantly, signaling along the GLP-1 receptor was shown to impinge on the canonical wingless-type integration (Wnt) pathway affecting 3T3-L1 pre-adipocytes differentiation and providing metabolic resilience in the face of increased calorie intake [174,175]. Namely, an enhancement of Wnt4 expression upon treatment with GLP-1 rescues β -catenin, the major transcription co-factor, from being exposed to cytosolic degradation by shuttling it to the cytoplasmic membrane [174].

On the other hand, treatment of high-fat diet-fed mice with liraglutide was reported to combat the suppression of Wnt signaling in epididymal fat tissues by rescuing the phosphorylation of β -catenin and its associated co-factor, transcription factor 7 like 2 (TCF7L2), an effect which is dependent on GLP-1 receptor [175]. This event was associated with a decrease in leptin along with an increase in adiponectin. A study by Mu et al. revealed that the latter is a direct effect of an increase in Sirt1/Foxo-1 signaling downstream GLP-1 receptor in adipose tissues, irrespective of a high-fat diet [176]. Interestingly, a similar increase in the phosphorylation of β -catenin and TCF7L2 was noticed upon *in vitro* treatment of stromal vascular fraction of mice epididymal fat tissues with liraglutide. Alternatively, GLP-1 receptor stimulation with liraglutide was found to enhance the proliferation and differentiation of murine C3H10T1/2 mesenchymal stem cells into brown adipocytes, further demonstrating a direct role for GLP-1 agonism in adipose tissue modulation in the face of metabolic challenge [177].

Conversely, in keeping with the differential function of canonical Wnt signaling in pre-mature/mature adipocytes versus adipocyte precursors [178], GLP-1 receptor stimulation was shown to exert opposite effects on the differentiation of human stem cells [179–181]. GLP-1 agonism suppresses the differentiation of bone marrow derived mesenchymal stem cells [179]. Additionally, GLP-1 receptor stimulation maintains stores of adipocyte precursors by increasing the mitotic proliferation of nondifferentiated bone marrow stem cells and decreasing their apoptosis [179].

On the other hand, GLP-1 receptor stimulation with liraglutide, *in vitro*, decreases the proliferation and induces the apoptosis of stem cells derived from human subcutaneous adipose tissues, also known as adipose-derived stem cells, while similarly limiting their differentiation [180–182]. Being the largest adipose depot with a characteristically high hyperplastic expansion capacity, the latter implicates a role for GLP-1 in resisting adiposity. Interestingly, it had been proposed that glycogen synthase kinase-3 (GSK-3), which phosphorylates β -catenin, mediates the effect of liraglutide on stem cell differentiation, as GSK-3 mRNA levels were shown to decrease, despite unaltered and rather elevated unphosphorylated and phosphorylated protein levels, respectively, in cells treated with liraglutide. Hence, these results collectively suggest that GLP-1 agonism combats obesity by limiting the genesis of adipocytes from stem cells, possibly reducing weight gain, and resists its deleterious consequences by recruiting potent pre-adipocytes into the differentiation process in an attempt to promote ‘healthy’ fat accumulation through hyperplasia rather than hypertrophy of pre-existing adipocytes.

Conclusion

SGLT-2i(s) and GLP-1 receptor agonists confer cardiovascular benefits by modulating adipose environments surrounding effector organs. The latter involves structural, functional, and metabolic changes of adipocytes and results in modification of inflammatory processes and resident immune cells. Adipose tissue modulation by SGLT-2i(s) and GLP-1 agonists is associated with improved cardiovascular structure and function. While studies linking the adipose regulatory effects of SGLT-2 inhibition to derived cardiovascular benefits are ample, evidence of the cardiovascular benefits of GLP-1 agonists mediated by amelioration of adipose tissue metabolism mostly originates indirectly from mechanistic findings of GLP-1 based interventions, i.e., dipeptidyl peptidase 4 inhibitors and GLP-1 overexpression by adenovirus. Thus, the investigation of the direct impact of available GLP-1 agonists on adipose tissue structure and function needs to be the focus of more research studies. Additionally, the origin of the depot-specificity in the effect of these drugs is worth further exploration. The variable expression levels of SGLT-2 and GLP-1 receptors in the different adipose beds in health and disease need to be investigated.

Notwithstanding the evidence of the mediating effect of adipose modulation in the cardioprotection offered by SGLT-2i(s) and GLP-1 receptor agonists, their direct cardiovascular and indirect systemic effects cannot be precluded [183]. Indeed, the GLP-1 receptor agonist efglenatide was recently shown to further improve the cardiovascular outcomes of diabetic patients on baseline SGLT-2i(s) [184]. Whether this additive effect is due to further adipose tissue modulation or superimposition of other mechanisms is not known. Interestingly, an amelioration of gut microbiota conferred by these drug classes can possibly mediate the relationship between adipose tissue and cardiovascular function in metabolic disease [185]. However, as the adipose modulatory effect proves to be paramount in the observed cardiovascular benefit of these drug classes, the need for further investigation to refine pharmacological properties, define eligible patients, and assess targeted monitoring and clinical endpoints will be required. Additionally, while the cardioprotection conferred by SGLT-2i(s) and GLP-1 receptor agonists seems to be dependent, at least in part, on their modulation on thoracic and visceral adipose depots, the contribution of their anti-obesogenic effects on brown and subcutaneous adipose beds to cardiovascular benefit cannot be ignored. Finally, differences between species in the pathology of metabolically-induced cardiovascular disease and the contribution of SGLT-2 and GLP-1 receptors, as well as in the responsiveness to SGLT-2i and GLP-1 agonists need to be taken into consideration in non-human

studies. Further, results from *ex vivo* experiments employing drug doses far beyond what is clinically relevant ought to be interpreted with caution.

Data Availability

NA

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRedit Author Contribution

Nour-Mounira Z. Bakkar: Writing—original draft. **Ibrahim AlZaim:** Writing—original draft. **Ahmed F. El-Yazbi:** Conceptualization, Resources, Supervision, Funding acquisition, Writing—review & editing.

Abbreviations

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; ECAT, epicardial adipose tissue; EDAT, epididymal adipose tissue; FABP4, fatty acid binding protein 4; GLP-1, glucagon-like peptide 1; GSK-3, glycogen synthase kinase-3; IAT, inguinal adipose tissue; MCP 1, monocyte chemoattractant protein 1; NF- κ B, nuclear factor-kappa B; PVAT, perivascular adipose tissue; SAT, subcutaneous adipose tissue; SGLT-2, sodium-glucose transporter 2; SIRT-1, sirtuin 1; T2D, Type 2 diabetic; TCF8L2, transcription factor 8 like 2; TNF- α , tumor necrosis factor- α ; UCP, uncoupling protein; VSMC, vascular smooth muscle cell; Wnt, wingless-type integration.

References

- Rafeh, R., Viveiros, A., Oudit, G.Y. and El-Yazbi, A.F. (2020) Targeting perivascular and epicardial adipose tissue inflammation: therapeutic opportunities for cardiovascular disease. *Clin. Sci. (Lond.)* **134**, 827–851, <https://doi.org/10.1042/CS20190227>
- Turnbull, F., Abraira, C., Anderson, R., Byington, R., Chalmers, J., Duckworth, W. et al. (2009) *Intensive glucose control and macrovascular outcomes in type 2 diabetes*, Springer
- Elkhatib, M.A., Mroueh, A., Rafeh, R.W., Sleiman, F., Fouad, H., Saad, E.I. et al. (2019) Amelioration of perivascular adipose inflammation reverses vascular dysfunction in a model of nonobese prediabetic metabolic challenge: potential role of antidiabetic drugs. *Transl. Res.* **214**, 121–143, <https://doi.org/10.1016/j.trsl.2019.07.009>
- Zinman, B., Wanner, C., Lachin, J.M., Fitchett, D., Bluhmki, E., Hantel, S. et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128, <https://doi.org/10.1056/NEJMoa1504720>
- Marso, S.P., Daniels, G.H., Brown-Frandsen, K., Kristensen, P., Mann, J.F.E., Nauck, M.A. et al. (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322, <https://doi.org/10.1056/NEJMoa1603827>
- Neal, B., Perkovic, V., Mahaffey, K.W., de Zeeuw, D., Fulcher, G., Erond, N. et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* **377**, 644–657, <https://doi.org/10.1056/NEJMoa1611925>
- McMurray, J.J.V., Solomon, S.D., Inzucchi, S.E., Køber, L., Kosiborod, M.N., Martinez, F.A. et al. (2019) Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **381**, 1995–2008, <https://doi.org/10.1056/NEJMoa1911303>
- Packer, M., Anker, S.D., Butler, J., Filippatos, G., Pocock, S.J., Carson, P. et al. (2020) Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J. Med.* **383**, 1413–1424, <https://doi.org/10.1056/NEJMoa2022190>
- Kaplan, A., Abidi, E., El-Yazbi, A., Eid, A., Booz, G.W. and Zoueiri, F.A. (2018) Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. *Heart Fail. Rev.* **23**, 419–437, <https://doi.org/10.1007/s10741-017-9665-9>
- Patel, D.K. and Strong, J. (2019) The pleiotropic effects of sodium–glucose cotransporter-2 inhibitors: beyond the glycaemic benefit. *Diab. Ther.* **10**, 1771–1792, <https://doi.org/10.1007/s13300-019-00686-z>
- Cowie, M.R. and Fisher, M. (2020) SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat. Rev. Cardiol.* **17**, 761–772, <https://doi.org/10.1038/s41569-020-0406-8>
- Costantino, S. and Paneni, F. (2019) GLP-1-based therapies to boost autophagy in cardiometabolic patients: From experimental evidence to clinical trials. *Vasc. Pharmacol.* **115**, 64–68, <https://doi.org/10.1016/j.vph.2019.03.003>
- Lajara, R. (2019) Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes. *Postgrad. Med.* **131**, 555–565, <https://doi.org/10.1080/00325481.2019.1670017>
- Elamin Abdelgadir, F.R., Bashier, A. and Ali, R. (2018) SGLT-2 inhibitors and cardiovascular protection: lessons and gaps in understanding the current outcome trials and possible benefits of combining SGLT-2 inhibitors with GLP-1 agonists. *J. Clin. Med. Res.* **10**, 615, <https://doi.org/10.14740/jocmr3467w>

- 15 Inzucchi, S.E., Kosiborod, M., Fitchett, D., Wanner, C., Hehne, U., Kaspers, S. et al. (2018) Improvement in cardiovascular outcomes with empagliflozin is independent of glycemic control. *Circulation* **138**, 1904–1907, <https://doi.org/10.1161/CIRCULATIONAHA.118.035759>
- 16 Sinha, B. and Ghosal, S. (2019) Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res. Clin. Pract.* **150**, 8–16, <https://doi.org/10.1016/j.diabres.2019.02.014>
- 17 Couselo-Seijas, M., Agra-Bermejo, R.M., Fernández, A.L., Martínez-Cereijo, J.M., Sierra, J., Soto-Pérez, M. et al. (2020) High released lactate by epicardial fat from coronary artery disease patients is reduced by dapagliflozin treatment. *Atherosclerosis* **292**, 60–69, <https://doi.org/10.1016/j.atherosclerosis.2019.11.016>
- 18 Zelniker, T.A., Wiviott, S.D., Raz, I., Im, K., Goodrich, E.L., Furtado, R.H. et al. (2019) Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus: systematic review and meta-analysis of cardiovascular outcomes trials. *Circulation* **139**, 2022–2031, <https://doi.org/10.1161/CIRCULATIONAHA.118.038868>
- 19 Bazzocchi, A., Diano, D., Ponti, F., Salizzoni, E., Albisinni, U., Marchesini, G. et al. (2014) A 360-degree overview of body composition in healthy people: relationships among anthropometry, ultrasonography, and dual-energy x-ray absorptiometry. *Nutrition* **30**, 696–701, <https://doi.org/10.1016/j.nut.2013.11.013>
- 20 Thanassoulis, G., Massaro, J.M., Corsini, E., Rogers, I., Schlett, C.L., Meigs, J.B. et al. (2012) Periaortic adipose tissue and aortic dimensions in the Framingham Heart Study. *J. Am. Heart Assoc.* **1**, e000885, <https://doi.org/10.1161/JAHA.112.000885>
- 21 Britton, K.A., Pedley, A., Massaro, J.M., Corsini, E.M., Murabito, J.M., Hoffmann, U. et al. (2012) Prevalence, distribution, and risk factor correlates of high thoracic periaortic fat in the Framingham Heart Study. *J. Am. Heart Assoc.* **1**, e004200, <https://doi.org/10.1161/JAHA.112.004200>
- 22 Lee, J.J., Pedley, A., Hoffmann, U., Massaro, J.M., Levy, D. and Long, M.T. (2018) Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the Framingham Heart Study. *Am. J. Med.* **131**, 684.e12–692.e12, <https://doi.org/10.1016/j.amjmed.2018.02.002>
- 23 Oikonomou, E.K. and Antoniades, C. (2019) The role of adipose tissue in cardiovascular health and disease. *Nat. Rev. Cardiol.* **16**, 83–99, <https://doi.org/10.1038/s41569-018-0097-6>
- 24 AlZaim, I., Hammoud, S.H., Al-Koussa, H., Ghazi, A., Eid, A.H. and El-Yazbi, A.F. (2020) Adipose tissue immunomodulation: a novel therapeutic approach in cardiovascular and metabolic diseases. *Front. Cardiovasc. Med.* **7**, 277, <https://doi.org/10.3389/fcvm.2020.602088>
- 25 Antonopoulos, A.S. and Tousoulis, D. (2017) The molecular mechanisms of obesity paradox. *Cardiovasc. Res.* **113**, 1074–1086, <https://doi.org/10.1093/cvr/cvx106>
- 26 Baglioni, S., Cantini, G., Poli, G., Francalanci, M., Squecco, R., Di Franco, A. et al. (2012) Functional differences in visceral and subcutaneous fat pads originate from differences in the adipose stem cell. *PLoS ONE* **7**, e36569, <https://doi.org/10.1371/journal.pone.0036569>
- 27 Fernández-Trasancos, Á., Fandiño-Vaquero, R., Agra, R.M., Fernández, Á.L., Viñuela, J.E., González-Juanatey, J.R. et al. (2014) Impaired adipogenesis and insulin resistance in epicardial fat-mesenchymal cells from patients with cardiovascular disease. *J. Cell. Physiol.* **229**, 1722–1730, <https://doi.org/10.1002/jcp.24619>
- 28 Tchkonja, T., Lenburg, M., Thomou, T., Giorgadze, N., Frampton, G., Pirtskhalava, T. et al. (2007) Identification of depot-specific human fat cell progenitors through distinct expression profiles and developmental gene patterns. *Am. J. Physiol.-Endocrinol. Metab.* **292**, E298–E307, <https://doi.org/10.1152/ajpendo.00202.2006>
- 29 Virdis, A., Duranti, E., Rossi, C., Dell’Agnello, U., Santini, E., Anselmino, M. et al. (2015) Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue. *Eur. Heart J.* **36**, 784–794, <https://doi.org/10.1093/eurheartj/ehu072>
- 30 Hammoud, S.H., AlZaim, I., Mougharbil, N., Koubar, S., Eid, A.H., Eid, A.A. et al. (2021) Peri-renal adipose inflammation contributes to renal dysfunction in a non-obese prediabetic rat model: Role of anti-diabetic drugs. *Biochem. Pharmacol.* **186**, 114491, <https://doi.org/10.1016/j.bcp.2021.114491>
- 31 Dwaib, H.S., Ajouz, G., AlZaim, I., Rafah, R., Mroueh, A., Mougharbil, N. et al. (2021) Phosphorus supplementation mitigates perivascular adipose inflammation-induced cardiovascular consequences in early metabolic impairment. *J. Am. Heart Assoc.* **10**, e023227, <https://doi.org/10.1161/JAHA.121.023227>
- 32 Horimatsu, T., Patel, A.S., Prasad, R., Reid, L.E., Benson, T.W., Zazour, A. et al. (2018) Remote effects of transplanted perivascular adipose tissue on endothelial function and atherosclerosis. *Cardiovasc. Drugs Ther.* **32**, 503–510, <https://doi.org/10.1007/s10557-018-6821-y>
- 33 Bakkar, N.-M.Z., Mougharbil, N., Mroueh, A., Kaplan, A., Eid, A.H., Fares, S. et al. (2020) Worsening baroreflex sensitivity on progression to type 2 diabetes: localized vs. systemic inflammation and role of antidiabetic therapy. *Am. J. Physiol.-Endocrinol. Metab.* **319**, E835–E851, <https://doi.org/10.1152/ajpendo.00145.2020>
- 34 Fried, S.K., Lee, M.J. and Karastergiou, K. (2015) Shaping fat distribution: new insights into the molecular determinants of depot-and sex-dependent adipose biology. *Obesity* **23**, 1345–1352, <https://doi.org/10.1002/oby.21133>
- 35 Lee, M.-J., Wu, Y. and Fried, S.K. (2013) Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. *Mol. Aspects Med.* **34**, 1–11, <https://doi.org/10.1016/j.mam.2012.10.001>
- 36 Ricquier, D. (2011) Uncoupling protein 1 of brown adipocytes, the only uncoupler: a historical perspective. *Front. Endocrinol.* **2**, 85, <https://doi.org/10.3389/fendo.2011.00085>
- 37 Pasarica, M., Sereda, O.R., Redman, L.M., Albarado, D.C., Hymel, D.T., Roan, L.E. et al. (2009) Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes* **58**, 718–725, <https://doi.org/10.2337/db08-1098>
- 38 Sacks, H.S. and Fain, J.N. (2007) Human epicardial adipose tissue: a review. *Am. Heart J.* **153**, 907–917, <https://doi.org/10.1016/j.ahj.2007.03.019>

- 39 Sacks, H.S., Fain, J.N., Holman, B., Cheema, P., Chary, A., Parks, F. et al. (2009) Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. *J. Clin. Endocrinol. Metab.* **94**, 3611–3615, <https://doi.org/10.1210/jc.2009-0571>
- 40 Bambace, C., Telesca, M., Zoico, E., Sepe, A., Olioso, D., Rossi, A. et al. (2011) Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men. *Cardiovasc. Pathol.* **20**, e153–e156, <https://doi.org/10.1016/j.carpath.2010.07.005>
- 41 Iacobellis, G. and Barbaro, G. (2019) Epicardial adipose tissue feeding and overfeeding the heart. *Nutrition* **59**, 1–6, <https://doi.org/10.1016/j.nut.2018.07.002>
- 42 Marchington, J.M. and Pond, C. (1990) Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. *Int. J. Obes.* **14**, 1013–1022
- 43 Burgeiro, A., Fuhrmann, A., Cherian, S., Espinoza, D., Jarak, I., Carvalho, R.A. et al. (2016) Glucose uptake and lipid metabolism are impaired in epicardial adipose tissue from heart failure patients with or without diabetes. *Am. J. Physiol.-Endocrinol. Metab.* **310**, E550–E564, <https://doi.org/10.1152/ajpendo.00384.2015>
- 44 Frayn, K. (2003) The glucose–fatty acid cycle: a physiological perspective. *Biochem. Soc. Trans.* **31**, 1115–1119, <https://doi.org/10.1042/bst0311115>
- 45 Kessler, G. and Friedman, J. (1998) Metabolism of fatty acids and glucose. *Circulation* **98**, 1350a–1353a, [https://doi.org/10.1161/circ.98.13.1350/a](https://doi.org/10.1161/circ.98.13.1350a)
- 46 Iacobellis, G. and Leonetti, F. (2005) Epicardial adipose tissue and insulin resistance in obese subjects. *J. Clin. Endocrinol. Metab.* **90**, 6300–6302, <https://doi.org/10.1210/jc.2005-1087>
- 47 Patel, V.B., Shah, S., Verma, S. and Oudit, G.Y. (2017) Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease. *Heart Fail. Rev.* **22**, 889–902, <https://doi.org/10.1007/s10741-017-9644-1>
- 48 Mahabadi, A.A., Berg, M.H., Lehmann, N., Kälsch, H., Bauer, M., Kara, K. et al. (2013) Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J. Am. Coll. Cardiol.* **61**, 1388–1395, <https://doi.org/10.1016/j.jacc.2012.11.062>
- 49 Wong, C.X., Ganesan, A.N. and Selvanayagam, J.B. (2017) Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur. Heart J.* **38**, 1294–1302
- 50 Khawaja, T., Greer, C., Chokshi, A., Chavarria, N., Thadani, S., Jones, M. et al. (2011) Epicardial fat volume in patients with left ventricular systolic dysfunction. *Am. J. Cardiol.* **108**, 397–401, <https://doi.org/10.1016/j.amjcard.2011.03.058>
- 51 Iacobellis, G. (2015) Local and systemic effects of the multifaceted epicardial adipose tissue depot. *Nat. Rev. Endocrinol.* **11**, 363–371, <https://doi.org/10.1038/nrendo.2015.58>
- 52 Díaz-Rodríguez, E., Agra, R.M., Fernández, Á.L., Adrio, B., García-Caballero, T., González-Juanatey, J.R. et al. (2018) Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc. Res.* **114**, 336–346, <https://doi.org/10.1093/cvr/cvx186>
- 53 Dozio, E., Vianello, E., Malavazos, A.E., Tacchini, L., Schmitz, G., Iacobellis, G. et al. (2019) 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.* **292**, 218–224, <https://doi.org/10.1016/j.ijcard.2019.04.039>
- 54 Iacobellis, G., Camarena, V., Sant, D.W. and Wang, G. (2017) Human epicardial fat expresses glucagon-like peptide 1 and 2 receptors genes. *Horm. Metab. Res.* **49**, 625–630, <https://doi.org/10.1055/s-0043-109563>
- 55 Antonopoulos, A.S. and Antoniadis, C. (2017) The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles. *J. Physiol.* **595**, 3907–3917, <https://doi.org/10.1113/JP273049>
- 56 Konwerski, M., Gaścecka, A., Opolski, G., Grabowski, M. and Mazurek, T. (2022) Role of epicardial adipose tissue in cardiovascular diseases: a review. *Biology* **11**, 355, <https://doi.org/10.3390/biology11030355>
- 57 Lin, Y.-K., Chen, Y.-C., Chen, J.-H., Chen, S.-A. and Chen, Y.-J. (2012) Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. *Basic Res. Cardiol.* **107**, 1–11, <https://doi.org/10.1007/s00395-012-0293-1>
- 58 Kocyigit, D., Gurses, K.M., Yalcin, M.U., Turk, G., Evranos, B., Yorgun, H. et al. (2015) Periatrial epicardial adipose tissue thickness is an independent predictor of atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation. *J. Cardiovasc. Comput. Tomogr.* **9**, 295–302, <https://doi.org/10.1016/j.jcct.2015.03.011>
- 59 Mahabadi, A.A., Lehmann, N., Kälsch, H., Bauer, M., Dykun, I., Kara, K. et al. (2014) Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: the Heinz Nixdorf Recall Study. *Eur. Heart J.—Cardiovasc. Imaging* **15**, 863–869, <https://doi.org/10.1093/ehjci/jeu006>
- 60 Ballasy, N.N., Jadli, A.S., Edalat, P., Kang, S., Fatehi Hassanabad, A., Gomes, K.P. et al. (2021) Potential role of epicardial adipose tissue in coronary artery endothelial cell dysfunction in type 2 diabetes. *FASEB J.* **35**, e21878, <https://doi.org/10.1096/fj.202100684RR>
- 61 Mari-Alexandre, J., Barceló-Molina, M., Sanz-Sánchez, J., Molina, P., Sancho, J., Abellán, Y. et al. (2019) Thickness and an altered miRNA expression in the epicardial adipose tissue is associated with coronary heart disease in sudden death victims. *Revista Española De Cardiología (English Edition)* **72**, 30–39, <https://doi.org/10.1016/j.rec.2017.12.007>
- 62 Vacca, M., Di Eusanio, M., Cariello, M., Graziano, G., D’Amore, S., Petridis, F.D. et al. (2016) Integrative miRNA and whole-genome analyses of epicardial adipose tissue in patients with coronary atherosclerosis. *Cardiovasc. Res.* **109**, 228–239, <https://doi.org/10.1093/cvr/cvw266>
- 63 Santos, D. and Carvalho, E. (2022) Adipose-related microRNAs as modulators of the cardiovascular system: the role of epicardial adipose tissue. *J. Physiol.* **600**, 1171–1187, <https://doi.org/10.1113/JP280917>
- 64 Blumensatt, M., Fahlbusch, P., Hilgers, R., Bekaert, M., Herzfeld de Wiza, D. et al. (2017) Secretory products from epicardial adipose tissue from patients with type 2 diabetes impair mitochondrial β -oxidation in cardiomyocytes via activation of the cardiac renin–angiotensin system and induction of miR-208a. *Basic Res. Cardiol.* **112**, 1–13, <https://doi.org/10.1007/s00395-016-0591-0>

- 65 Greulich, S., de Wiza, D.H., Preilowski, S., Ding, Z., Mueller, H., Langin, D. et al. (2011) Secretory products of guinea pig epicardial fat induce insulin resistance and impair primary adult rat cardiomyocyte function. *J. Cell. Mol. Med.* **15**, 2399–2410, <https://doi.org/10.1111/j.1582-4934.2010.01232.x>
- 66 Greulich, S., Maxhera, B., Vandenplas, G., de Wiza, D.H., Smiris, K., Mueller, H. et al. (2012) Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation* **126**, 2324–2334, <https://doi.org/10.1161/CIRCULATIONAHA.111.039586>
- 67 Venticlef, N., Guglielmi, V., Balse, E., Gaborit, B., Cotillard, A., Atassi, F. et al. (2015) Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokinases. *Eur. Heart J.* **36**, 795–805, <https://doi.org/10.1093/eurheartj/ehu099>
- 68 Blumensatt, M., Greulich, S., Herzfeld de Wiza, D., Mueller, H., Maxhera, B. et al. (2013) Activin A impairs insulin action in cardiomyocytes via up-regulation of miR-143. *Cardiovasc. Res.* **100**, 201–210, <https://doi.org/10.1093/cvr/cvt173>
- 69 Ng, A.C., Strudwick, M., van der Geest, R.J., Ng, A.C., Gillinder, L., Goo, S.Y. et al. (2018) Impact of epicardial adipose tissue, left ventricular myocardial fat content, and interstitial fibrosis on myocardial contractile function. *Circulation: Cardiovasc. Imaging* **11**, e007372, <https://doi.org/10.1161/CIRCIMAGING.117.007372>
- 70 Jiang, D.-S., Zeng, H.-L., Li, R., Huo, B., Su, Y.-S., Fang, J. et al. (2017) Aberrant epicardial adipose tissue extracellular matrix remodeling in patients with severe ischemic cardiomyopathy: insight from comparative quantitative proteomics. *Sci. Rep.* **7**, 1–12, <https://doi.org/10.1038/srep43787>
- 71 Nesti, L., Pugliese, N.R., Chiriaco, M., Trico, D., Baldi, S. and Natali, A. (2022) Epicardial adipose tissue thickness is associated with reduced peak oxygen consumption and systolic reserve in patients with type 2 diabetes and normal heart function. *Diab. Obesity Metab.*, <https://doi.org/10.1111/dom.14861>
- 72 Nakanishi, K., Fukuda, S., Tanaka, A., Otsuka, K., Jissho, S., Taguchi, H. et al. (2014) Persistent epicardial adipose tissue accumulation is associated with coronary plaque vulnerability and future acute coronary syndrome in non-obese subjects with coronary artery disease. *Atherosclerosis* **237**, 353–360, <https://doi.org/10.1016/j.atherosclerosis.2014.09.015>
- 73 Takahara, S., Ferdaoussi, M., Srnec, N., Maayah, Z.H., Soni, S., Migglautsch, A.K. et al. (2021) Inhibition of ATGL in adipose tissue ameliorates isoproterenol-induced cardiac remodeling by reducing adipose tissue inflammation. *Am. J. Physiol.-Heart Circulatory Physiol.* **320**, H432–H446, <https://doi.org/10.1152/ajpheart.00737.2020>
- 74 Vianello, E., Dozio, E., Bandera, F., Froidl, M., Micaglio, E., Lamont, J. et al. (2020) Correlative study on impaired prostaglandin E2 regulation in epicardial adipose tissue and its role in maladaptive cardiac remodeling via EPAC2 and ST2 signaling in overweight cardiovascular disease subjects. *Int. J. Mol. Sci.* **21**, 520, <https://doi.org/10.3390/ijms21020520>
- 75 Antonopoulos, A.S., Margaritis, M., Verheule, S., Recalde, A., Sanna, F., Herdman, L. et al. (2016) Mutual regulation of epicardial adipose tissue and myocardial redox state by PPAR- γ /adiponectin signalling. *Circ. Res.* **118**, 842–855, <https://doi.org/10.1161/CIRCRESAHA.115.307856>
- 76 Rachwalik, M., Zyśko, D., Diakowska, D. and Kustrzycki, W. (2014) Increased content of resistin in epicardial adipose tissue of patients with advanced coronary atherosclerosis and history of myocardial infarction. *Thorac. Cardiovasc. Surg.* **62**, 554–560, <https://doi.org/10.1055/s-0034-1376403>
- 77 Karastergiou, K., Evans, I., Ogston, N., Miheisi, N., Nair, D., Kaski, J.-C. et al. (2010) Epicardial adipokines in obesity and coronary artery disease induce atherogenic changes in monocytes and endothelial cells. *Arteriosclerosis, Thrombosis Vasc. Biol.* **30**, 1340–1346, <https://doi.org/10.1161/ATVBAHA.110.204719>
- 78 Xia, N. and Li, H. (2017) The role of perivascular adipose tissue in obesity-induced vascular dysfunction. *Br. J. Pharmacol.* **174**, 3425–3442, <https://doi.org/10.1111/bph.13650>
- 79 Kim, H.W., Belin de Chantemèle, E.J. and Weintraub, N.L. (2019) Perivascular adipocytes in vascular disease. *Arteriosclerosis, Thrombosis Vasc. Biol.* **39**, 2220–2227, <https://doi.org/10.1161/ATVBAHA.119.312304>
- 80 Aghamohammadzadeh, R., Unwin, R.D., Greenstein, A.S. and Heagerty, A.M. (2015) Effects of obesity on perivascular adipose tissue vasorelaxant function: nitric oxide, inflammation and elevated systemic blood pressure. *J. Vasc. Res.* **52**, 299–305, <https://doi.org/10.1159/000443885>
- 81 Greenstein, A.S., Khavandi, K., Withers, S.B., Sonoyama, K., Clancy, O., Jeziorska, M. et al. (2009) Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. *Circulation* **119**, 1661–1670, <https://doi.org/10.1161/CIRCULATIONAHA.108.821181>
- 82 Yudkin, J.S., Eringa, E. and Stehouwer, C.D. (2005) “Vasocrine” signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet North Am. Ed.* **365**, 1817–1820, [https://doi.org/10.1016/S0140-6736\(05\)66585-3](https://doi.org/10.1016/S0140-6736(05)66585-3)
- 83 Al-Assi, O., Ghali, R., Mroueh, A., Kaplan, A., Mougharbil, N., Eid, A.H. et al. (2018) Cardiac autonomic neuropathy as a result of mild hypercaloric challenge in absence of signs of diabetes: modulation by antidiabetic drugs. *Oxidative Med. Cell. Longevity* **2018**, <https://doi.org/10.1155/2018/9389784>
- 84 Kumar, R.K., Yang, Y., Contreras, A.G., Garver, H., Bhattacharya, S., Fink, G.D. et al. (2021) Phenotypic changes in T cell and macrophage subtypes in perivascular adipose tissues precede high-fat diet-induced hypertension. *Front. Physiol.* **12**, 616055, <https://doi.org/10.3389/fphys.2021.616055>
- 85 Mikolajczyk, T.P., Nosalski, R., Szczepaniak, P., Budzyn, K., Osmenda, G., Skiba, D. et al. (2016) Role of chemokine RANTES in the regulation of perivascular inflammation, T-cell accumulation, and vascular dysfunction in hypertension. *FASEB J.* **30**, 1987–1999, <https://doi.org/10.1096/fj.201500088R>
- 86 Payne, G.A., Borbouse, L.N., Kumar, S., Neeb, Z., Alloosh, M., Sturek, M. et al. (2010) Epicardial perivascular adipose-derived leptin exacerbates coronary endothelial dysfunction in metabolic syndrome via a protein kinase C- β pathway. *Arteriosclerosis Thrombosis Vasc. Biol.* **30**, 1711–1717, <https://doi.org/10.1161/ATVBAHA.110.210070>
- 87 Xia, N., Horke, S., Habermeyer, A., Closs, E.I., Reifenberg, G., Gericke, A. et al. (2016) Uncoupling of endothelial nitric oxide synthase in perivascular adipose tissue of diet-induced obese mice. *Arteriosclerosis, Thrombosis Vasc. Biol.* **36**, 78–85, <https://doi.org/10.1161/ATVBAHA.115.306263>
- 88 Uchida, Y., Uchida, Y., Shimoyama, E., Hiruta, N., Kishimoto, T. and Watanabe, S. (2016) Pericoronary adipose tissue as storage and supply site for oxidized low-density lipoprotein in human coronary plaques. *PLoS ONE* **11**, e0150862, <https://doi.org/10.1371/journal.pone.0150862>

- 89 Gil-Ortega, M., Condezo-Hoyos, L., García-Prieto, C.F., Arribas, S.M., González, M.C., Aranguéz, I. et al. (2014) Imbalance between pro and anti-oxidant mechanisms in perivascular adipose tissue aggravates long-term high-fat diet-derived endothelial dysfunction. *PLoS ONE* **9**, e95312, <https://doi.org/10.1371/journal.pone.0095312>
- 90 Procopio, C., Andreozzi, F., Laratta, E., Cassese, A., Beguinot, F., Arturi, F. et al. (2009) Leptin-stimulated endothelial nitric-oxide synthase via an adenosine 5'-monophosphate-activated protein kinase/Akt signaling pathway is attenuated by interaction with C-reactive protein. *Endocrinology* **150**, 3584–3593, <https://doi.org/10.1210/en.2008-0921>
- 91 Chatterjee, T.K., Aronow, B.J., Tong, W.S., Manka, D., Tang, Y., Bogdanov, V.Y. et al. (2013) Human coronary artery perivascular adipocytes overexpress genes responsible for regulating vascular morphology, inflammation, and hemostasis. *Physiol. Genomics* **45**, 697–709, <https://doi.org/10.1152/physiolgenomics.00042.2013>
- 92 Vasamsetti, S.B., Natarajan, N., Sadaf, S., Florentin, J. and Dutta, P. (2022) Regulation of cardiovascular health and disease by visceral adipose tissue-derived metabolic hormones. *J. Physiol.*, <https://doi.org/10.1113/JP282728>
- 93 Sawaki, D., Czibik, G., Pini, M., Ternacle, J., Suffee, N., Mercedes, R. et al. (2018) Visceral adipose tissue drives cardiac aging through modulation of fibroblast senescence by osteopontin production. *Circulation* **138**, 809–822, <https://doi.org/10.1161/CIRCULATIONAHA.117.031358>
- 94 Xie, Z., Wang, X., Liu, X., Du, H., Sun, C., Shao, X. et al. (2018) Adipose-derived exosomes exert proatherogenic effects by regulating macrophage foam cell formation and polarization. *J. Am. Heart Assoc.* **7**, e007442, <https://doi.org/10.1161/JAHA.117.007442>
- 95 Gutiérrez-Tenorio, J., Marín-Royo, G., Martínez-Martínez, E., Martín, R., Miana, M., López-Andrés, N. et al. (2017) The role of oxidative stress in the crosstalk between leptin and mineralocorticoid receptor in the cardiac fibrosis associated with obesity. *Sci. Rep.* **7**, 1–9, <https://doi.org/10.1038/s41598-017-17103-9>
- 96 Figueroa, A.L., Takx, R.A., MacNabb, M.H., Abdelbaky, A., Lavender, Z.R., Kaplan, R.S. et al. (2016) Relationship between measures of adiposity, arterial inflammation, and subsequent cardiovascular events. *Circulation: Cardiovasc. Imaging* **9**, e004043, <https://doi.org/10.1161/CIRCIMAGING.115.004043>
- 97 Huby, A.-C., Antonova, G., Groenendyk, J., Gomez-Sanchez, C.E., Bollag, W.B., Filosa, J.A. et al. (2015) Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation* **132**, 2134–2145, <https://doi.org/10.1161/CIRCULATIONAHA.115.018226>
- 98 Huang, Y., Liu, Y., Ma, Y., Tu, T., Liu, N., Bai, F. et al. (2022) Associations of visceral adipose tissue, circulating protein biomarkers, and risk of cardiovascular diseases: a mendelian randomization analysis. *Front. Cell Development. Biol.* **10**, 840866, <https://doi.org/10.3389/fcell.2022.840866>
- 99 Jensky, N.E., Criqui, M.H., Wright, C.M., Wassel, C.L., Alcaraz, J.E. and Allison, M.A. (2011) The association between abdominal body composition and vascular calcification. *Obesity* **19**, 2418–2424, <https://doi.org/10.1038/oby.2011.70>
- 100 Hanzu, F., Palomo, M., Kalko, S., Parrizas, M., Garaulet, M., Escobar, G. et al. (2011) Translational evidence of endothelial damage in obese individuals: inflammatory and prothrombotic responses. *J. Thromb. Haemost.* **9**, 1236–1245, <https://doi.org/10.1111/j.1538-7836.2011.04285.x>
- 101 Bemelmans, R.H., Van Der Graaf, Y., Nathoe, H.M., Wassink, A.M., Vernooij, J.W. et al. (2012) Increased visceral adipose tissue is associated with increased resting heart rate in patients with manifest vascular disease. *Obesity* **20**, 834–841, <https://doi.org/10.1038/oby.2011.321>
- 102 Lee, Y.-C., Chang, H.-H., Chiang, C.-L., Liu, C.-H., Yeh, J.-I., Chen, M.-F. et al. (2011) Role of perivascular adipose tissue-derived methyl palmitate in vascular tone regulation and pathogenesis of hypertension. *Circulation* **124**, 1160–1171, <https://doi.org/10.1161/CIRCULATIONAHA.111.027375>
- 103 Margaritis, M., Antonopoulos, A.S., Digby, J., Lee, R., Reilly, S., Coutinho, P. et al. (2013) Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. *Circulation* **127**, 2209–2221, <https://doi.org/10.1161/CIRCULATIONAHA.112.001133>
- 104 Ayala-Lopez, N., Thompson, J.M. and Watts, S.W. (2017) Perivascular adipose tissue's impact on norepinephrine-induced contraction of mesenteric resistance arteries. *Front. Physiol.* **8**, 37, <https://doi.org/10.3389/fphys.2017.00037>
- 105 Chatterjee, T.K., Stoll, L.L., Denning, G.M., Harrelson, A., Blomkalns, A.L., Idelman, G. et al. (2009) Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ. Res.* **104**, 541–549, <https://doi.org/10.1161/CIRCRESAHA.108.182998>
- 106 Henrichot, E., Juge-Aubry, C.E., Pernin, A., Pache, J.-C., Velebit, V., Dayer, J.-M. et al. (2005) Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? *Arterioscler. Thromb. Vasc. Biol.* **25**, 2594–2599, <https://doi.org/10.1161/01.ATV.0000188508.40052.35>
- 107 Aghamohammadzadeh, R., Greenstein, A.S., Yadav, R., Jeziorska, M., Hama, S., Soltani, F. et al. (2013) Effects of bariatric surgery on human small artery function: evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. *J. Am. Coll. Cardiol.* **62**, 128–135, <https://doi.org/10.1016/j.jacc.2013.04.027>
- 108 Sardu, C., D'Onofrio, N., Torella, M., Portoghese, M., Mureddu, S., Loreni, F. et al. (2021) Metformin therapy effects on the expression of sodium-glucose cotransporter 2, leptin, and sirt6 levels in pericoronary fat excised from pre-diabetic patients with acute myocardial infarction. *Biomedicine* **9**, 904, <https://doi.org/10.3390/biomedicine9080904>
- 109 Fox, C.S., Massaro, J.M., Hoffmann, U., Pou, K.M., Maurovich-Horvat, P., Liu, C.-Y. et al. (2007) Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* **116**, 39–48, <https://doi.org/10.1161/CIRCULATIONAHA.106.675355>
- 110 Wajchenberg, B.L. (2000) Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr. Rev.* **21**, 697–738, <https://doi.org/10.1210/edrv.21.6.0415>
- 111 Virtue, S. and Vidal-Puig, A. (2010) Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective. *Biochim Biophys Acta* **1801**, 338–349, <https://doi.org/10.1016/j.bbali.2009.12.006>
- 112 Khan, T., Muise, E.S., Iyengar, P., Wang, Z.V., Chandalia, M., Abate, N. et al. (2009) Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. *Mol. Cell. Biol.* **29**, 1575–1591, <https://doi.org/10.1128/MCB.01300-08>

- 113 Shi, H., Kokoeva, M.V., Inouye, K., Tzameli, I., Yin, H. and Flier, J.S. (2006) TLR4 links innate immunity and fatty acid–induced insulin resistance. *J. Clin. Invest.* **116**, 3015–3025, <https://doi.org/10.1172/JCI28898>
- 114 Crewe, C., An, Y.A. and Scherer, P.E. (2017) The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. *J. Clin. Invest.* **127**, 74–82, <https://doi.org/10.1172/JCI88883>
- 115 Sun, K., Asterholm, I.W., Kusminski, C.M., Bueno, A.C., Wang, Z.V., Pollard, J.W. et al. (2012) Dichotomous effects of VEGF-A on adipose tissue dysfunction. *Proc. Natl. Acad. Sci.* **109**, 5874–5879, <https://doi.org/10.1073/pnas.1200447109>
- 116 Rutkowski, J.M., Stern, J.H. and Scherer, P.E. (2015) The cell biology of fat expansion. *J. Cell Biol.* **208**, 501–512, <https://doi.org/10.1083/jcb.201409063>
- 117 Kumar, D., Shankar, K., Patel, S., Gupta, A., Varshney, S., Gupta, S. et al. (2018) Chronic hyperinsulinemia promotes meta-inflammation and extracellular matrix deposition in adipose tissue: Implications of nitric oxide. *Mol. Cell. Endocrinol.* **477**, 15–28, <https://doi.org/10.1016/j.mce.2018.05.010>
- 118 Antonopoulos, A.S., Margaritis, M., Coutinho, P., Digby, J., Patel, R., Psarros, C. et al. (2014) Reciprocal effects of systemic inflammation and brain natriuretic peptide on adiponectin biosynthesis in adipose tissue of patients with ischemic heart disease. *Arteriosclerosis Thrombosis Vasc. Biol.* **34**, 2151–2159, <https://doi.org/10.1161/ATVBAHA.114.303828>
- 119 Wang, Q.A., Tao, C., Gupta, R.K. and Scherer, P.E. (2013) Tracking adipogenesis during white adipose tissue development, expansion and regeneration. *Nat. Med.* **19**, 1338–1344, <https://doi.org/10.1038/nm.3324>
- 120 Min, S.Y., Kady, J., Nam, M., Rojas-Rodriguez, R., Berkenwald, A., Kim, J.H. et al. (2016) Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. *Nat. Med.* **22**, 312–318, <https://doi.org/10.1038/nm.4031>
- 121 Bouchi, R., Terashima, M., Sasahara, Y., Asakawa, M., Fukuda, T., Takeuchi, T. et al. (2017) Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: a pilot study. *Cardiovasc. Diabetol.* **16**, 1–9, <https://doi.org/10.1186/s12933-017-0516-8>
- 122 Sato, T., Aizawa, Y., Yuasa, S., Kishi, S., Fuse, K., Fujita, S. et al. (2018) The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc. Diabetol.* **17**, 1–9, <https://doi.org/10.1186/s12933-017-0658-8>
- 123 Yagi, S., Hirata, Y., Ise, T., Kusunose, K., Yamada, H., Fukuda, D. et al. (2017) Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus. *Diabetol. Metab. Syndrome* **9**, 1–7, <https://doi.org/10.1186/s13098-017-0275-4>
- 124 Iacobellis, G. and Gra-Menendez, S. (2020) Effects of dapagliflozin on epicardial fat thickness in patients with type 2 diabetes and obesity. *Obesity* **28**, 1068–1074, <https://doi.org/10.1002/oby.22798>
- 125 St-Pierre, J., Lin, J., Krauss, S., Tarr, P.T., Yang, R., Newgard, C.B. et al. (2003) Bioenergetic analysis of peroxisome proliferator-activated receptor γ coactivators 1 α and 1 β (PGC-1 α and PGC-1 β) in muscle cells. *J. Biol. Chem.* **278**, 26597–26603, <https://doi.org/10.1074/jbc.M301850200>
- 126 Sato, T., Aizawa, Y., Yuasa, S., Fujita, S., Ikeda, Y. and Okabe, M. (2020) The effect of dapagliflozin treatment on epicardial adipose tissue volume and P-wave indices: an ad-hoc analysis of the previous randomized clinical trial. *J. Atheroscler. Thromb.* **27**, 48009, <https://doi.org/10.5551/jat.48009>
- 127 Bakkar, N.-M.Z., Dwaib, H.S., Fares, S., Eid, A.H., Al-Dhaheiri, Y. and El-Yazbi, A.F. (2020) Cardiac autonomic neuropathy: a progressive consequence of chronic low-grade inflammation in type 2 diabetes and related metabolic disorders. *Int. J. Mol. Sci.* **21**, 9005, <https://doi.org/10.3390/ijms21239005>
- 128 Fares, S.A., Bakkar, N.-M.Z. and El-Yazbi, A.F. (2022) Predictive capacity of beat-to-beat blood pressure variability for cardioautonomic and vascular dysfunction in early metabolic challenge. *Front. Pharmacol.* **13**, <https://doi.org/10.3389/fphar.2022.902582>
- 129 Mori, K., Tsuchiya, K., Nakamura, S., Miyachi, Y., Shiba, K., Ogawa, Y. et al. (2019) Ipragliflozin-induced adipose expansion inhibits cuff-induced vascular remodeling in mice. *Cardiovasc. Diabetol.* **18**, 1–12, <https://doi.org/10.1186/s12933-019-0886-1>
- 130 Mori, Y., Terasaki, M., Hiromura, M., Saito, T., Kushima, H., Koshibu, M. et al. (2019) Luseogliflozin attenuates neointimal hyperplasia after wire injury in high-fat diet-fed mice via inhibition of perivascular adipose tissue remodeling. *Cardiovasc. Diabetol.* **18**, 1–9, <https://doi.org/10.1186/s12933-019-0947-5>
- 131 Lim, J., Park, H.S., Kim, J., Jang, Y.J., Kim, J.-H., Lee, Y. et al. (2020) Depot-specific UCP1 expression in human white adipose tissue and its association with obesity-related markers. *Int. J. Obes.* **44**, 697–706, <https://doi.org/10.1038/s41366-020-0528-4>
- 132 Saxton, S.N., Heagerty, A.M. and Withers, S.B. (2020) Perivascular adipose tissue: an immune cell metropolis. *Exp. Physiol.* **105**, 1440–1443, <https://doi.org/10.1113/EP087872>
- 133 Dwaib, H.S., Ajouz, G., AlZaim, I., Rafeh, R., Mroueh, A., Mougharbil, N. et al. (2021) Phosphorus supplementation mitigates perivascular adipose inflammation–induced cardiovascular consequences in early metabolic impairment. *J. Am. Heart Assoc.* **10**, e023227, <https://doi.org/10.1161/JAHA.121.023227>
- 134 Nojima, T., Matsubayashi, Y., Yoshida, A., Suganami, H., Abe, T., Ishizawa, M. et al. (2020) Influence of an SGLT2 inhibitor, tofogliflozin, on the resting heart rate in relation to adipose tissue insulin resistance. *Diabet. Med.* **37**, 1316–1325, <https://doi.org/10.1111/dme.14279>
- 135 Nguyen, T., Wen, S., Gong, M., Yuan, X., Xu, D., Wang, C. et al. (2020) Dapagliflozin activates neurons in the central nervous system and regulates cardiovascular activity by inhibiting SGLT-2 in mice. *Diab. Metab. Syndrome Obesity* **13**, 2781, <https://doi.org/10.2147/DMSO.S258593>
- 136 Thayer, J. and Fischer, J. (2009) Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. *J. Intern. Med.* **265**, 439–447, <https://doi.org/10.1111/j.1365-2796.2008.02023.x>
- 137 Hammoud, S., AlZaim, I., Bekdash, A., Mougharbil, N., Itani, H.A. and El-Yazbi, A.F. (2021) Abstract 9725: autonomic modulation mitigates perivascular and perirenal adipose inflammation and consequent cardiorenal involvement in prediabetes. *Circulation* **144**, A9725–A, https://doi.org/10.1161/circ.144.suppl_1.9725
- 138 Yang, X., Liu, Q., Li, Y., Ding, Y., Zhao, Y., Tang, Q. et al. (2021) Inhibition of the sodium–glucose co-transporter SGLT2 by canagliflozin ameliorates diet-induced obesity by increasing intra-adipose sympathetic innervation. *Br. J. Pharmacol.* **178**, 1756–1771, <https://doi.org/10.1111/bph.15381>
- 139 Chiba, Y., Yamada, T., Tsukita, S., Takahashi, K., Munakata, Y., Shirai, Y. et al. (2016) Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, acutely reduces energy expenditure in BAT via neural signals in mice. *PLoS ONE* **11**, e0150756, <https://doi.org/10.1371/journal.pone.0150756>

- 140 Naznin, F., Sakoda, H., Okada, T., Tsubouchi, H., Waise, T.Z., Arakawa, K. et al. (2017) Canagliflozin, a sodium glucose cotransporter 2 inhibitor, attenuates obesity-induced inflammation in the nodose ganglion, hypothalamus, and skeletal muscle of mice. *Eur. J. Pharmacol.* **794**, 37–44, <https://doi.org/10.1016/j.ejphar.2016.11.028>
- 141 Sa-Nguanmoo, P., Tanajak, P., Kerdphoo, S., Jaiwongkam, T., Pratchayasakul, W., Chattipakorn, N. et al. (2017) SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. *Toxicol. Appl. Pharmacol.* **333**, 43–50, <https://doi.org/10.1016/j.taap.2017.08.005>
- 142 Lim, V.G., He, H., Lachlan, T., Ng, G.A., Kyrou, I., Randevo, H.S. et al. (2022) Impact of sodium-glucose co-transporter inhibitors on cardiac autonomic function and mortality: no time to die. *EP Europace* **24**, 1052–1057, <https://doi.org/10.1093/europace/euab321>
- 143 Miyachi, Y., Tsuchiya, K., Shiba, K., Mori, K., Komiya, C., Ogasawara, N. et al. (2018) A reduced M1-like/M2-like ratio of macrophages in healthy adipose tissue expansion during SGLT2 inhibition. *Sci. Rep.* **8**, 1–13, <https://doi.org/10.1038/s41598-018-34305-x>
- 144 Choi, R.H., Tatum, S.M., Symons, J.D., Summers, S.A. and Holland, W.L. (2021) Ceramides and other sphingolipids as drivers of cardiovascular disease. *Nat. Rev. Cardiol.* 1–11, <https://doi.org/10.1038/s41569-021-00536-1>
- 145 Xu, L., Nagata, N., Nagashimada, M., Zhuge, F., Ni, Y., Chen, G. et al. (2017) 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* **20**, 137–149, <https://doi.org/10.1016/j.ebiom.2017.05.028>
- 146 Kusaka, H., Koibuchi, N., Hasegawa, Y., Ogawa, H. and Kim-Mitsuyama, S. (2016) Empagliflozin lessened cardiac injury and reduced visceral adipocyte hypertrophy in prediabetic rats with metabolic syndrome. *Cardiovasc. Diabetol.* **15**, 1–14, <https://doi.org/10.1186/s12933-016-0473-7>
- 147 De Stefano, A., Tesaro, M., Di Daniele, N., Vizioli, G., Schinzari, F. and Cardillo, C. (2021) Mechanisms of SGLT2 (sodium-glucose transporter type 2) inhibition-induced relaxation in arteries from human visceral adipose tissue. *Hypertension* **77**, 729–738, <https://doi.org/10.1161/HYPERTENSIONAHA.120.16466>
- 148 Okuma, H., Mori, K., Nakamura, S., Sekine, T., Ogawa, Y. and Tsuchiya, K. (2021) Ipragliflozin ameliorates diabetic nephropathy associated with perirenal adipose expansion in mice. *Int. J. Mol. Sci.* **22**, 7329, <https://doi.org/10.3390/ijms22147329>
- 149 Iacobellis, G., Mohseni, M., Bianco, S.D. and Banga, P.K. (2017) Liraglutide causes large and rapid epicardial fat reduction. *Obesity* **25**, 311–316, <https://doi.org/10.1002/oby.21718>
- 150 Morano, S., Romagnoli, E., Filardi, T., Nieddu, L., Mandosi, E., Fallarino, M. et al. (2015) Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study. *Acta Diabetol.* **52**, 727–732, <https://doi.org/10.1007/s00592-014-0710-z>
- 151 Akawi, N., Checa, A., Akoumianakis, I., Farid, S., Srivastava, V., Krasopoulos, G. et al. (2021) Liraglutide improves myocardial redox state in humans by regulating the adipose tissue-derived long-chain ceramides. *Circulation* **144**, A13393–A, <https://doi.org/10.1161/circ.144.suppl.2.13393>
- 152 Akawi, N., Checa, A., Antonopoulos, A.S., Akoumianakis, I., Daskalaki, E., Kotanidis, C.P. et al. (2021) Fat-secreted ceramides regulate vascular redox state and influence outcomes in patients with cardiovascular disease. *J. Am. Coll. Cardiol.* **77**, 2494–2513, <https://doi.org/10.1016/j.jacc.2021.03.314>
- 153 Jendle, J., Hyötyläinen, T., Orešič, M. and Nyström, T. (2021) Pharmacometabolomic profiles in type 2 diabetic subjects treated with liraglutide or glimepiride. *Cardiovasc. Diabetol.* **20**, 1–12, <https://doi.org/10.1186/s12933-021-01431-2>
- 154 Alaaeddine, R., Elkhatib, M.A., Mroueh, A., Fouad, H., Saad, E.I., El-Sabban, M.E. et al. (2019) Impaired endothelium-dependent hyperpolarization underlies endothelial dysfunction during early metabolic challenge: Increased ROS generation and possible interference with NO function. *J. Pharmacol. Exp. Ther.* **371**, 567–582, <https://doi.org/10.1124/jpet.119.262048>
- 155 Han, F., Hou, N., Liu, Y., Huang, N., Pan, R., Zhang, X. et al. (2019) Liraglutide improves vascular dysfunction by regulating a cAMP-independent PKA-AMPK pathway in perivascular adipose tissue in obese mice. *Biomed. Pharmacotherapy* **120**, 109537, <https://doi.org/10.1016/j.biopha.2019.109537>
- 156 Chen, X., Huang, Q., Feng, J., Xiao, Z., Zhang, X. and Zhao, L. (2021) GLP-1 alleviates NLRP3 inflammasome-dependent inflammation in perivascular adipose tissue by inhibiting the NF- κ B signalling pathway. *J. Int. Med. Res.* **49**, 0300060521992981, <https://doi.org/10.1177/0300060521992981>
- 157 Zhu, B., Li, Y., Mei, W., He, M., Ding, Y., Meng, B. et al. (2019) Alogliptin improves endothelial function by promoting autophagy in perivascular adipose tissue of obese mice through a GLP-1-dependent mechanism. *Vasc. Pharmacol.* **115**, 55–63, <https://doi.org/10.1016/j.vph.2018.11.003>
- 158 Richards, P., Parker, H.E., Adriaenssens, A.E., Hodgson, J.M., Cork, S.C., Trapp, S. et al. (2014) Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. *Diabetes* **63**, 1224–1233, <https://doi.org/10.2337/db13-1440>
- 159 Lee, Y.-S., Park, M.-S., Choung, J.-S., Kim, S.-S., Oh, H.-H., Choi, C.-S. et al. (2012) Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia* **55**, 2456–2468, <https://doi.org/10.1007/s00125-012-2592-3>
- 160 Chen, J., Zhao, H., Ma, X., Zhang, Y., Lu, S., Wang, Y. et al. (2017) GLP-1/GLP-1R signaling in regulation of adipocyte differentiation and lipogenesis. *Cell. Physiol. Biochem.* **42**, 1165–1176, <https://doi.org/10.1159/000478872>
- 161 Rodrigues, T., Borges, P., Mar, L., Marques, D., Albano, M., Eickhoff, H. et al. (2020) GLP-1 improves adipose tissue glyoxalase activity and capillarization improving insulin sensitivity in type 2 diabetes. *Pharmacol. Res.* **161**, 105198, <https://doi.org/10.1016/j.phrs.2020.105198>
- 162 Matafome, P., Rodrigues, T., Sena, C. and Seça, R. (2017) Methylglyoxal in metabolic disorders: facts, myths, and promises. *Med. Res. Rev.* **37**, 368–403, <https://doi.org/10.1002/med.21410>
- 163 Matafome, P., Santos-Silva, D., Crisóstomo, J., Rodrigues, T., Rodrigues, L., Sena, C. et al. (2012) Methylglyoxal causes structural and functional alterations in adipose tissue independently of obesity. *Arch. Physiol. Biochem.* **118**, 58–68, <https://doi.org/10.3109/13813455.2012.658065>
- 164 Rodrigues, T., Matafome, P. and Seça, R. (2013) Methylglyoxal further impairs adipose tissue metabolism after partial decrease of blood supply. *Arch. Physiol. Biochem.* **119**, 209–218, <https://doi.org/10.3109/13813455.2013.812121>
- 165 Rodrigues, T., Matafome, P., Sereno, J., Almeida, J., Castelhana, J., Gamas, L. et al. (2017) Methylglyoxal-induced glycation changes adipose tissue vascular architecture, flow and expansion, leading to insulin resistance. *Sci. Rep.* **7**, 1–13, <https://doi.org/10.1038/s41598-017-01730-3>

- 166 Wan, Y., Bao, X., Huang, J., Zhang, X., Liu, W., Cui, Q. et al. (2017) Novel GLP-1 analog supaglutide reduces HFD-induced obesity associated with increased Ucp-1 in white adipose tissue in mice. *Front. Physiol.* **8**, 294, <https://doi.org/10.3389/fphys.2017.00294>
- 167 Xu, F., Lin, B., Zheng, X., Chen, Z., Cao, H., Xu, H. et al. (2016) GLP-1 receptor agonist promotes brown remodelling in mouse white adipose tissue through SIRT1. *Diabetologia* **59**, 1059–1069, <https://doi.org/10.1007/s00125-016-3896-5>
- 168 Jiang, Y., Wang, Z., Ma, B., Fan, L., Yi, N., Lu, B. et al. (2018) GLP-1 improves adipocyte insulin sensitivity following induction of endoplasmic reticulum stress. *Front. Pharmacol.* **9**, 1168, <https://doi.org/10.3389/fphar.2018.01168>
- 169 Bugáňová, M., Pelantová, H., Holubová, M., Šedivá, B., Maletínská, L., Železná, B. et al. (2017) The effects of liraglutide in mice with diet-induced obesity studied by metabolomics. *J. Endocrinol.* **233**, 93–104, <https://doi.org/10.1530/JOE-16-0478>
- 170 Zhu, E., Yang, Y., Zhang, J., Li, Y., Li, C., Chen, L. et al. (2016) Liraglutide suppresses obesity and induces brown fat-like phenotype via Soluble Guanylyl Cyclase mediated pathway in vivo and in vitro. *Oncotarget* **7**, 81077, <https://doi.org/10.18632/oncotarget.13189>
- 171 Gerstein, H.C., Sattar, N., Rosenstock, J., Ramasundharahettige, C., Pratley, R., Lopes, R.D. et al. (2021) Cardiovascular and renal outcomes with epeglenatide in type 2 diabetes. *N. Engl. J. Med.* **385**, 896–907, <https://doi.org/10.1056/NEJMoa2108269>
- 172 Challa, T.D., Beaton, N., Arnold, M., Rudofsky, G., Langhans, W. and Wolfrum, C. (2012) Regulation of adipocyte formation by GLP-1/GLP-1R signaling. *J. Biol. Chem.* **287**, 6421–6430, <https://doi.org/10.1074/jbc.M111.310342>
- 173 Yang, J., Ren, J., Song, J., Liu, F., Wu, C., Wang, X. et al. (2013) Glucagon-like peptide 1 regulates adipogenesis in 3T3-L1 preadipocytes. *Int. J. Mol. Med.* **31**, 1429–1435, <https://doi.org/10.3892/ijmm.2013.1350>
- 174 Liu, R., Li, N., Lin, Y., Wang, M., Peng, Y., Lewi, K. et al. (2016) Glucagon like peptide-1 promotes adipocyte differentiation via the Wnt4 mediated sequestering of beta-catenin. *PLoS ONE* **11**, e0160212, <https://doi.org/10.1371/journal.pone.0160212>
- 175 Gu, J., Shao, W., Liu, D., Feng, J.N., Pang, J. and Jin, T. (2022) Liraglutide stimulates the β -catenin signaling cascade in mouse epididymal fat tissue. *J. Mol. Endocrinol.* **69**, 343–356, <https://doi.org/10.1530/JME-22-0026>
- 176 Wang, A., Li, T., An, P., Yan, W., Zheng, H., Wang, B. et al. (2017) Exendin-4 upregulates adiponectin level in adipocytes via Sirt1/Foxo-1 signaling pathway. *PLoS ONE* **12**, e0169469, <https://doi.org/10.1371/journal.pone.0169469>
- 177 Wang, X., Chen, J., Rong, C., Pan, F., Zhao, X. and Hu, Y. (2018) GLP-1RA promotes brown adipogenesis of C3H10T1/2 mesenchymal stem cells via the PI3K-AKT-mTOR signaling pathway. *Biochem. Biophys. Res. Commun.* **506**, 976–982, <https://doi.org/10.1016/j.bbrc.2018.10.197>
- 178 Chen, N. and Wang, J. (2018) Wnt/ β -catenin signaling and obesity. *Front. Physiol.* **9**, 792, <https://doi.org/10.3389/fphys.2018.00792>
- 179 Sanz, C., Vazquez, P., Blazquez, C., Barrio, P., Alvarez, M.D.M. and Blazquez, E. (2010) Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow. *Am. J. Physiol.-Endocrinol. Metab.* **298**, E634–E643, <https://doi.org/10.1152/ajpendo.00460.2009>
- 180 Liu, H., Zhan, Y.-I., Luo, G.-j., Zou, L.-I, Li, Y. and Lu, H.-y (2020) Liraglutide and insulin have contrary effects on adipogenesis of human adipose-derived stem cells via wnt pathway. *Diab. Metabolic Syndrome Obesity* **13**, 3075, <https://doi.org/10.2147/DMSO.S253097>
- 181 Cantini, G., Di Franco, A., Samavat, J., Forti, G., Mannucci, E. and Luconi, M. (2015) Effect of liraglutide on proliferation and differentiation of human adipose stem cells. *Mol. Cell. Endocrinol.* **402**, 43–50, <https://doi.org/10.1016/j.mce.2014.12.021>
- 182 Cantini, G., Di Franco, A., Mannucci, E. and Luconi, M. (2017) Is cleaved glucagon-like peptide 1 really inactive? Effects of GLP-1 (9–36) on human adipose stem cells. *Mol. Cell. Endocrinol.* **439**, 10–15, <https://doi.org/10.1016/j.mce.2016.10.013>
- 183 Bonnet, F. and Scheen, A. (2018) Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diab. Metab.* **44**, 457–464, <https://doi.org/10.1016/j.diabet.2018.09.005>
- 184 Lam, C.S.P., Ramasundharahettige, C., Branch, K.R.H., Sattar, N., Rosenstock, J., Pratley, R. et al. (2022) Epeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation* **145**, 565–574, <https://doi.org/10.1161/CIRCULATIONAHA.121.057934>
- 185 Lee, D.M., Battson, M.L., Jarrell, D.K., Hou, S., Ecton, K.E., Weir, T.L. et al. (2018) SGLT2 inhibition via dapagliflozin improves generalized vascular dysfunction and alters the gut microbiota in type 2 diabetic mice. *Cardiovasc. Diabetol.* **17**, 1–14, <https://doi.org/10.1186/s12933-018-0708-x>