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Review article

Epicardial adipose tissue feeding and overfeeding the heart

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ABSTRACT

Epicardial adipose tissue is a particular visceral fat depot with unique anatomic, biomolecular, and genetic features. Epicardial fat displays both physiological and pathological properties. Epicardial fat expresses genes and secretes cytokines actively involved in the thermogenesis and regulation of lipid and glucose metabolism of the adjacent myocardium. A disequilibrium between epicardial fat feeding and overfeeding the myocardium with free fatty acids leads to intramyocardial fat infiltration causing organ damage and clinical consequences. The upregulation of epicardial fat proinflammatory and lipogenic genes contributes to the fat build up in the proximal coronary arteries. Epicardial fat is a measurable and modifiable risk factor that can serve as a novel and additional tool for cardiovascular risk stratification. Pharmacologically targeting epicardial fat with drugs such as glucagon peptide-like 1 analogs or sodium glucose transport 2 inhibitors reduces the epicardial fat burden and induces beneficial cardiometabolic effects. Assessment and manipulation of epicardial fat transcriptome might open new avenues in the prevention of cardiometabolic diseases.

Introduction

From being a finding of mainly anatomical interest, epicardial adipose tissue has recently emerged as the main actor in the cardiovascular scene [1–3]. It is believed that epicardial fat actively plays a role in the development and progression of coronary artery disease (CAD) and more recently atrial fibrillation (AF). Given its imaging measurability and fast responsiveness to fat-targeted pharmacological agents, epicardial fat is considered a novel diagnostic marker and therapeutic target in cardiometabolic diseases, including diabetes and obesity [4–6]. In this review, we provide an overview of epicardial fat from a different angle. As in a delicate equilibrium, epicardial fat can feed, but more often overfeed the heart, leading to serious organ damage and clinical consequences, as depicted in Figure 1. Hence, we focus on the nutritional features, such as its involvement with lipid and glucose metabolism, of both healthy and sick epicardial fat and its effect on clinical practice.

Anatomy of the epicardial adipose tissue

Epicardial adipose tissue is a unique visceral fat depot with anatomic and functional proximity to the heart. Epicardial fat and intra-abdominal fat share the same embryogenesis and both evolve from brown fat [1,2]. Macroscopically, epicardial adipose tissue represents ~20% of the heart mass. Several factors, such as genetic profile, ethnicity, sex, and environment, influence epicardial fat volume [1,7]. Epicardial fat is indeed differently distributed within the heart and can be located within the myocardium, around the coronary arteries, ventricles, and atria. Epicardial adipose tissue lies between the myocardium and the visceral layer of the pericardium and has to be differentiated by the pericardial fat, located externally of the myocardium [8]. Microscopically, epicardial fat is composed of mainly adipocytes, smaller than those located in subcutaneous and other visceral fat depots, but also inflammatory, vascular, and neural cells [9,10]. Epicardial fat cells are generally smaller with more abundant preadipocytes than mature adipocytes because of a high-consuming metabolism that may prevent large lipid storage [9,10]. Epicardial fat is supplied by branches of the coronary arteries and no muscle fascia separates the fat depot and the myocardium. There are evidences of a microcirculatory connection between the epicardial fat and the coronary wall via vasa vasora. As the two tissues share the same microcirculation, a direct crosstalk between the fat and the myocardium has been highly suggested [1–3]. Paracrine release of cytokines from periadventitial epicardial fat could traverse the coronary wall by diffusion from outside to inside. Alternatively, cytokines might be released from epicardial tissue directly into vasa vasorum and be transported downstream into the arterial wall in a vasocrine-signaling mechanism.

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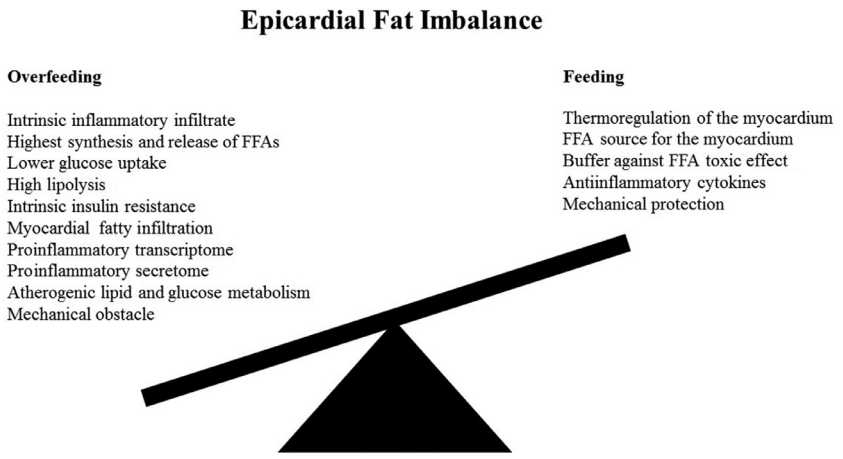

Fig. 1. Schematic of the delicate equilibrium of epicardial fat between physiological and pathologic properties. FFA, free fatty acid.

Epicardial adipose tissue feeding and heating the heart

Between physiology and pathology

Epicardial fat is a paracrine fat depot with peculiar genetic, biomolecular, and anatomic properties. Epicardial fat is actively involved in lipid and energy homeostasis, serving as both lipid storage and a local source of energy by channeling free fatty acids (FFAs) to the myocardium [11]. Epicardial fat displays the greatest capacity for FFAs release and uptake and lower rate of glucose utilization, among any other visceral fat depots. In fact, FFA synthesis, rate of incorporation and breakdown, and rates of lipolysis and insulin-induced lipogenesis are higher in epicardial fat than in other visceral fat depots [11]. Insulin increases the rate of lipogenesis but not that of fatty acid incorporation in epicardial fat [11]. Myocardium uses and metabolizes FFAs from the coronary arterial blood, and FFA oxidation is responsible for ~70% of the heart's energy production. Physiologically, epicardial adipose tissue works as a buffer, absorbing FFAs and protecting the heart against the toxic effect of excessively high fatty acids levels. The high basal rates of fatty acid incorporation and lipogenesis of epicardial fat serves as a rapidly mobilizable energy store for the myocardium. Given the proximity to the heart, owing to the absence of muscle fascia that separates the two tissues, FFAs are transported from the epicardial fat directly into the myocardium. FFAs can diffuse bidirectionally in interstitial fluid across concentration gradients. Epicardial adipose tissue also secretes vasoactive factors that regulate coronary arterial tone and so facilitate the FFAs influx. Fatty acid–binding protein 4, highly expressed in epicardial fat, participates in the intracellular transport of FFAs from epicardial fat into the myocardium [12]. Epicardial fat expresses and secretes adiponectin, an adipocyte-derived cytokines that contributes to fatty acid combustion. Remarkably, adiponectin gene and protein expression in patients with CAD is downregulated [13]. The lower epicardial fat adiponectin expression can therefore contribute to favor FFAs myocardial accumulation over combustion. Compared with subcutaneous adipose tissue, human epicardial fat is rich in saturated fatty acids [14], such as myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0), whereas unsaturated fatty acids are lower. This profound difference in fatty acid composition accounts for the different rate of mobilization, deposition, and synthesis of FFAs between epicardial and subcutaneous fat.

Under physiological conditions, epicardial fat displays metabolic, mechanical, and brown fat-like activity to protect the myocardium against hypothermia [15]. Brown adipose tissue generates heat in response to cold temperatures and activation of the autonomic nervous system. Brown fat activation would be the ideal fat burner and therefore weight loss mediator, but unfortunately most of the brown fat is lost in the transition from infancy to adult life in humans. However, recent studies have suggested unexpected brown fat properties of the human epicardial fat. In fact, brown adipose tissue–specific gene uncoupling protein-1 (*UCP-1*) and other brown fat–related genes, such as brown adipocyte differentiation transcription factors PR domain–missing 16 (*PRDM16*) and peroxisome proliferator–activated receptor γ co-activator-1 alpha (*PGC-1 α*), are all highly expressed in human epicardial fat [15]. *UCP-1* is significantly higher in human epicardial fat than other fat depots and basically undetectable in subcutaneous fat. *UCP-1* expression and overall brown fat-like activity of epicardial fat seems to be downregulated in advanced CAD [16]. Although these recent findings are intriguing, the role of epicardial fat to serve as brown fat to the myocardium is still unclear. Epicardial fat could provide direct heating to the myocardium and protect the heart during a drop in core body temperature or during unfavorable hemodynamic conditions, such as ischemia or hypoxia. Animal models may support this working hypothesis. In fact, polar bears present large amounts of cardiac fat that can be used to store and supply energy to the myocardium during hibernation [9]. How and whether these observations can be translated to humans is unknown. Epicardial fat is generally considered a white adipose tissue. Remarkably, epicardial adipocyte may also have brown fat-like or beige fat features, as recently suggested. In fact, small unilocular adipocytes without *UCP-1* immunostaining have been described in epicardial fat, suggesting some histologic similarities with those described in vitro in beige lineage adipocytes [17]. In cases of hypothermia, chronic exposure to cold promotes epicardial fat peroxisome proliferator γ coactivator 1 α (*PPARγC1 α*) activation, a key mediator of the white-to-beige adipocyte transformation [17]. Epicardial fat may adapt itself to different metabolic circumstance and function as brown or beige fat depot as needed. Nevertheless, whether epicardial fat is a brown fat or it can function as brown fat–like depot is unclear and also a topic of discussion.

Epicardial adipose tissue overfeeding the heart

Epicardial fat myocardial lipotoxicity

Epicardial fat is higher in experimental animals and in obese individuals who were fed high-fat diets, particularly in those presenting with excessive abdominal adiposity. However, intracellular

ectopic fat infiltration seems to be even more important than general obesity or intraabdominal visceral adiposity. Intraorgan fatty infiltration is associated with end-organ damages and increased cardiovascular risk [18]. Ectopic fat deposition also occurs within the heart and may cause a metabolic cardiomyopathy. Excessive epicardial adipose tissue can produce lipotoxic effects throughout an abnormal lipid deposition and fatty infiltration in the myocardium. As cardiomyocyte fat storage capacity is very limited, high levels of plasma lipids cause cardiac steatosis, dysfunction, and ultimately failure, as observed in morbid obesity and uncontrolled diabetes [19]. High-fat feeding increases the rate of fatty acid incorporation in all adipose depots [9]. An imbalanced diet can affect gut microbiome and consequently influence adipose tissue, including epicardial fat, and metabolism [20]. Pericardial and epicardial adipose tissue respond similarly to high-fat feeding, but the magnitude of the response is greater in the epicardial fat depot [9]. An independent and significant relation of epicardial fat, as measured with echocardiography, and intramyocardial lipid content, as measured by proton magnetic resonance spectroscopy has been described [21]. Myocardial lipid content increases with the degree of adiposity and may contribute to the adverse structural and functional cardiac adaptations seen in obese individuals. The increased myocardial triacylglycerol content can be considered a result of the FFA overload and saturation of the physiological FFA oxidative capacity by the heart [19]. Intramyocardial FFAs undergo peroxidation and saturation, leading to the accumulation of fatty acid intermediates in the cytoplasm and functional damage to the heart. Excessive release of FFAs from the epicardial fat into the cardiomyocytes recently has been evoked as contributory to the development and progression of AF [2]. FFAs can be transported from the peri-atrial epicardial fat to the left atrium and lead to electromechanical changes in atrial tissue, favouring the break through and re-entry of electrical impulses. Increased epicardial fat could also influence the intrinsic autonomic system, increasing the propensity for AF.

Epicardial fat lipid atherogenicity

Epicardial fat plays an important role in the development and progression of coronary atherosclerosis, as emerged only in the past decade. The mechanisms underlying the atherogenicity of epicardial fat are complex and also involve the lipid homeostasis. Epicardial fat inflammation, innate immunity response, and lipid metabolism are closely interrelated. Human epicardial fat displays a dense, intrinsic inflammatory infiltrate, characterized mostly by proinflammatory M1 macrophages and mast cells [22]. Toll-like receptors (TLRs), located within epicardial fat macrophages and adipocytes are activated in response to excessive FFAs, recognized as endogenous antigens. This leads to an upregulation of transcription factors, such as *NF-κB* and *FOS,* and their translocation into the nucleus of epicardial adipocytes. The upregulation of these transcription factors causes an overexpression of epicardial fat inflammatory factors such as interleukin (IL)-1, IL-8, IL-6, and tumor necrosis factor (TNF)-α. Inflammatory mediators then activate macrophages derived from transdifferentiated adipocytes, inducing lipolysis and upregulation of intracellular adhesion molecule-1 (ICAM-1), IL-6, and monocyte chemoattractant protein-1 (MCP-1), ultimately leading to the lipid accumulation within the atherosclerotic plaque. Lipase G (*LIPG*), solute carrier family 7 member 5 (*SLC7 A5*), and solute carrier family 16 member 10 (*SLC16 A10*), all involved in lipid metabolism and nutrient transport, are among the top upregulated genes in diabetic epicardial fat [16]. Epicardial fat is also highly enriched in secretory type II phospholipase A2 ($sPLA_2$-IIA or PLA2 G2 A), the rate-limiting enzyme in the synthesis of proinflammatory lipid mediator [23]. The upregulation of $sPLA_2$ is certainly an additional factor contributing to the lipid build up in the coronary arteries. The lipogenic effect of epicardial fat also has been attributed to its highest fat content of conjugated fatty acids [14].

Epicardial fat glucose atherogenicity

Diabetes is a major and well-known risk factor of coronary atherosclerosis. If insulin resistance and hyperglycemia are traditional players, epicardial fat emerged as a novel and multifaceted factor. The paracrine secretion of epicardial inflammatory molecules contributes to the metabolic and inflammatory milieu that promotes atherosclerosis and cardiac changes in diabetes. Epicardial fat per se can be considered a relatively insulin-resistant fat depot. In fact, the rate of insulin-stimulated lipogenesis in epicardial fat tissue is significantly greater than other visceral fat depots, but insulin had little or no effects on the incorporation and glucose uptake of epicardial fat fatty acids [11]. Epicardial adipose tissue glucose utilization is about half that of the intra-abdominal fat depots in monkeys [9]. Diabetic epicardial fat transcriptome is unique and markedly different from that of subcutaneous fat, suggesting a novel atherogenic pathway in diabetes, as recently reported [24]. Omentin (*ITLN1*) is the most upregulated gene and secreted adipokine in both diabetic and not diabetic epicardial fat [16,24]. RNA-sequencing analysis showed that diabetic epicardial fat is highly enriched in genes involved in inflammation. Upregulated genes in diabetic epicardial fat included different pathways of the inflammatory response, such as cytokine production, leukocyte migration, cytokine–cytokine interaction, innate inflammatory response, and *AGE-RAGE* signaling [24]. Gene-enrichment analysis of transcription factors showed that expression of diabetic epicardial fat genes is mostly due to the action of upregulated transcription factors, such as those belonging to *NF-κB* family and *FOS* family [24]. Epicardial fat could also contribute to create a local coronary insulin resistance. Interestingly, glucose transporter-4 (GLUT4) mRNA levels are lower in epicardial fat, whereas renitol-binding protein 4 (RBP4) is higher than those in subcutaneous fat in patients with CAD [25]. Epicardial fat fatty acid composition is also peculiar in patients with diabetes. Diabetic epicardial fat shows a significant increase in unsaturated fatty acids 12:0 and 16:0 and a significant decrease in unsaturated fatty acid 20:4 ω-6 levels [14]. Epicardial fat in patients with diabetes displays a significant decrease of palmitic acid (16:0) level and ω-3 fatty acids (20:5 ω-3 and 22:6 ω-3) and their precursor, 18:2 ω-6, and increase of trans fatty acids and conjugated fatty acids that could contribute to the diabetic cardiomyopathy mediated by excessive epicardial fat. Diabetic epicardial fat glucose and lipid metabolism are closely interrelated. Epicardial fat endothelial *LIPG* is upregulated in diabetes, as recently reported [24]. *LIPG* is a gene involved in the lipid uptake and endothelium regulation and may contribute to the pathogenesis of diabetic cardiomyopathy. Diabetic epicardial fat is highly enriched in *GOS2*, another protein-coding gene, considered one of the target genes of peroxisome proliferator-activated receptor (PPAR)α and PPARγ [26] which are transcription factors involved in the regulation of lipid metabolism, mitochondrial fatty acid oxidation, inflammation, and immunity. Epicardial fat overexpression of low-density lipoprotein receptor-related protein 1 and very low-density lipoprotein receptor has been recently suggested to play a role diabetic dyslipidemia [27]. Notably, a recent study pointed out a role of epicardial fat in type 1 diabetes possibly mediated by leptin [28]. Remarkably, epicardial adipocytes size has been correlated with serum leptin levels [10]. The lipotoxic effects of palmitate, highly enriched in diabetic epicardial

fat, could increase serum soluble leptin receptor levels and consequently circulating leptin levels.

Clinical consequences of the overfeeding epicardial adipose tissue

Epicardial fat is measurable risk factor that can be detected and assessed with standard imaging techniques. Echocardiography [4–6], provides a simple, accurate, and readily available measurement of epicardial fat thickness (Fig. 2); whereas computed tomography allows a precise assessment of pericoronary or periatrial epicardial fat volume, but a more expensive and cumbersome measurement [29]. Regardless of how it is measured, epicardial fat is a marker of visceral adiposity, rather than overall obesity [5]. Echocardiographic epicardial fat strongly and independently reflects the intra-abdominal visceral fat and intramyocardial triacylglycerol content, as measured by proton magnetic resonance spectroscopy [20]. Ultrasound-measured epicardial fat also is related to liver steatosis and surrogate markers of fatty liver [30]. Epicardial fat, regardless of how it is assessed, is associated with higher cardiometabolic risk, metabolic syndrome, presence and severity of CAD, and subclinical atherosclerosis [31–33]. Different cutoff points of epicardial fat thickness were proposed to predict metabolic syndrome, although ethnicity and sex can influence these threshold values and no consensus has yet to be reached [33]. Epicardial fat is a predictor of fatal and nonfatal coronary events in the general population, regardless of the traditional cardiovascular risk factors [34,35]. Epicardial fat, whether measured as thickness or volume, has been significantly correlated with the extent and severity of CAD, chest pain, unstable angina, and ST elevation myocardial infarction [36]. It has been recently reported that epicardial fat is an independent predictor of the progression and development of AF even after adjusting for other traditional AF risk factors [37–39]. Epicardial adipose tissue could contribute to the fibrosis of neighboring atrial myocardium by secreting inflammatory cytokine profibrotic factors and activin A [39].

Epicardial fat thickness is higher in individuals with prediabetes and type 2 diabetes, in those with and without atherosclerosis, and also in patients with type 1 diabetes [40–42]. Epicardial fat thickness is inversely associated with insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamp and other markers of insulin resistance, in adults and adolescents without diabetes [43]. Excessive epicardial fat, either thickness or volume, has been associated with cardiac changes, such as increased left ventricular mass, abnormal right ventricle geometry, and enlarged atria in individuals with obesity and diabetes [44,45]. Mechanical and biomolecular mechanisms can explain these correlations. Larger epicardial fat pad can mechanically affect ventricular work and progressively lead to a maladaptive ventricular hypertrophy. Epicardial fat profibrotic and proinflammatory cytokines can directly affect the cardiomyocytes and ultimately cause anatomic and functional changes. The intense secretory profile of epicardial fat may contribute to the pathogenesis of diabetes mellitus–related cardiomyopathy [46]. Epicardial fat also can affect the diastolic function in individuals with diabetes and obesity, because of the mechanical obstacle to both filling and relaxation caused by the excessive fat pad.

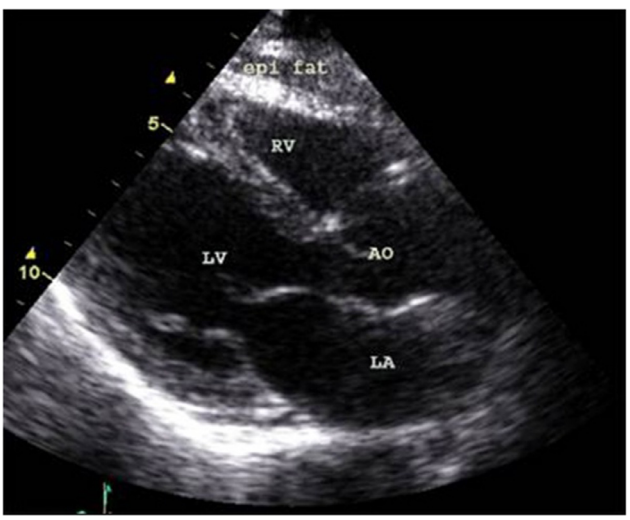

Fig. 2. Echocardiographic parasternal long-axis view of epicardial fat thickness, the echo free space within the arrows, according to the method first described by Iacobellis et al. [4–6]. AO, aorta; epi, epicardial; LA, left atrium; LV, left ventricle; RV, right ventricle.

Interventions targeting the epicardial adipose tissue

Epicardial fat is a not only a measurable, but also is a modifiable risk factor. In fact, because of its intrinsic rapid metabolism and simple objective measurability, epicardial fat can serve as a therapeutic target for interventions directly or indirectly targeting the adipose tissue. Earlier and selective visceral fat reduction has been recently thought to be a key factor in the metabolic improvement that follows a weight loss. Hence, epicardial fat changes were evaluated after different weight loss interventions. Epicardial fat has shown to reduce after very low-calorie diet and bariatric surgery, although postbariatric surgery effects were more modest [47–49]. Bariatric surgery causes a large fat mass reduction, whereas epicardial fat seems to be more sensitive to a direct intervention. On the contrary, ultrasound-measured epicardial fat thickness significantly and quickly decreased after a very low-calorie diet in morbidly obese individuals [47]. Remarkably, the magnitude of epicardial fat reduction when following a low-calorie diet was higher and faster than that of body mass index and waist circumference [47]. Changes in epicardial fat thickness were consensually and independently associated with the improvement in cardiac parameters in these individuals. Epicardial fat changed with moderate aerobic exercise, but in a lesser extent than weight loss [50]. The effect of pharmacologic agents on epicardial fat appears to be more specific and clinically meaningful. The role of the glucagon-like peptide 1 analog (GLP-1 A) liraglutide on epicardial fat thickness was tested in a 24-wk interventional case-controlled study in overweight or obese type 2 diabetic individuals on metformin monotherapy [51]. Ultrasound-measured epicardial fat thickness decreased after 12 and 24 wk, respectively, accounting for an unprecedented 36% of reduction at 24 wk, whereas there was no significant epicardial fat reduction in the metformin group. Epicardial fat shrunk independently of overall weight loss and improved glucose control. A milder, yet noticeable (−13%), reduction of epicardial fat thickness was also observed after 12 wk of treatment either with either liraglutide or exenatide [52]. There was no significant difference between the two GLP-1 As. Remarkably, it has been recently discovered that human epicardial fat expressed the GLP-1 receptor (*GLP-1 R*) gene and mRNA expression, supporting the hypothesis of a direct effect of the GLP-1 agonism [53]. *GLP-1 R* expression was no different between diabetics and nondiabetics, suggesting the need for a broader use of GLP-1-analogs targeting the fat. GLP-1 activation can improve local insulin sensitivity and metabolism by promoting preadipocyte differentiation and browning thermogenesis of epicardial fat [54,55]. Epicardial fat thickness responded and significantly decreased also on sitagliptin, a dipeptidyl peptidase-4

inhibitor (DPP4 i) [56]. DPP4 i treatment increased the brown fat activity in mice who were fed a high-fat diet [57]. Selective sodium-glucose cotransporter 2 inhibitors is a new class of antidiabetic agents that could induce a clinically meaningful weight loss. Treatment with dapagliflozin, canagliflozin, and other selective sodium-glucose cotransporter 2 inhibitors has shown to decrease epicardial fat volume and thickness in patients with type 2 diabetes [58–60]. In particular, dapagliflozin increased glucose uptake, reduced the secretion of proinflammatory chemokines, and improved the differentiation of epicardial fat adipocytes [60]. The effects of statins and glitazones on epicardial fat also have been explored. Epicardial fat thickness and volume decreased with atorvastatin better than with simvastatin [61,62]. The effect of atorvastatin on epicardial fat was independent of lipid-lowering agents or progression of CAD. Pioglitazone caused a significant reduction of the expression of epicardial fat inflammatory cytokines such as IL-1 β [63]. PPARγ agonist induced a rapid browning of the epicardial fat in experimental models [64]. Rosiglitazone treatment caused a significant upregulation of PPARγ coactivator 1-α, a key precursor of brown fat, in epicardial adipocytes of Zucker rats. Interestingly, *GLP-2 R* gene and mRNA expression recently have been found in epicardial fat [53]. *GLP-2* activation could induce beneficial effects on the glucose homeostasis and insulin sensitivity, although its role is still under evaluation. Insulin and metformin induced no or modest changes in the epicardial fat [65].

Future perspectives

Future studies are warranted to further and better understand the biomolecular and genetic features of epicardial fat and its role in CAD, AF, and diabetes. Imaging of epicardial fat could become a routine tool to stratify and predict the cardiometabolic risk for high-risk patients. Echocardiographic assessment of epicardial fat could serve as first-step, noninvasive, and readily accessible standard-of-care procedure. Computed tomography imaging could be a second-step approach for a volumetric and more accurate epicardial fat mapping. Pharmacologically targeting epicardial fat may induce beneficial cardiovascular and metabolic effects. Genetic manipulation of epicardial fat transcriptome could open new avenues in the prevention of cardiovascular diseases.

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