Effects of antidiabetic drugs on epicardial fat

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Abstract

Epicardial adipose tissue is defined as a deposit of adipocytes with pathophysiological properties similar to those of visceral fat, located in the space between the myocardial muscle and the pericardial sac. When compared with subcutaneous adipose tissue, visceral adipocytes show higher metabolic activity, lipolysis rates, increased insulin resistance along with more steroid hormone receptors. The epicardial adipose tissue interacts with numerous cardiovascular pathways *via* vasocrine and paracrine signalling comprised of pro- and anti-inflammatory cytokines excretion. Both the physiological differences between the two tissue types, as well as the fact that fat distribution and phenotype, rather than quantity, affect cardiovascular function and metabolic processes, establish epicardial fat as a biomarker for cardiovascular and metabolic syndrome. Numerous studies have underlined an association of altered epicardial fat morphology, type 2 diabetes mellitus (T2DM) and adverse cardiovascular events. In this review, we explore the prospect of using the epicardial adipose tissue as a therapeutic target in T2DM and describe the underlying mechanisms by which the antidiabetic drugs affect the pathophysiological processes induced from adipose tissue accumulation and possibly allow for more favourable cardiovascular outcomes though epicardial fat manipulation.

Key words: Epicardial fat; Adipose tissue; Type 2 diabetes mellitus; Antidiabetic drugs

Core tip: In this review, we aim to create a concise overview of the pathophysiology concerning the epicardial fat deposits on a type 2 diabetic individual, while, delving into the intricacies of each antidiabetic drug and exploring the manner by which it interacts with visceral fat accumulation in the sub-pericardial space.

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INTRODUCTION

Subcutaneous (SCAT) and visceral adipose tissue (VAT) are two extremely heterogenous tissue types, differentiated by anatomical, molecular, cellular, physiological and clinical characteristics[1]. Researchers have suggested that the variation of composition and function of the two tissue types is induced very early in the tissue developmental pathway, as a result of adipose stem cell distinction[2]. VAT has an anatomically distinct distribution in the mesentery and omentum, when compared to SCAT that is mainly located in the femerogluteal area, back and abdominal wall[1]. As a result of the anatomical differences, vascularization and innervation vary between the tissues, with VAT having superior nerve and vascular networks, as well as draining into the portal system of veins. Based on the aforementioned anatomical link, the "portal theory" of metabolic inflammation states that free fatty acids and pro-inflammatory molecules from VAT, interact with the liver, promoting hepatocellular dysfunction in the form of insulin resistance and steatosis[3]. The dissimilarity in cellular composition between SCAT and VAT is a result of divergent ratio of large to small adipocytes between the two tissues. Large, metabolically dysfunctional, adipocytes, predominate in VAT, while SCAT is mainly composed by small adipocytes with higher free fatty acids and triglycerides capacity and increased insulin sensitivity[4,5]. The signaling pathways activated in the two tissue types vary due to a shift in receptor distribution and adipokine synthesis[1]. Glucocorticoid and androgen receptors present with a higher density in VAT while oestrogen receptors are more active in SCAT. Adrenergic signaling patterns are distinct for the two cell populations, with VAT being more β_3- and α_2- adrenoreceptor sensitive[6]. The biologically active molecules produced by the adipose tissue, referred to as adipokines, are formed and released at different rates between VAT and SCAT. Adipokines are the basis of adipose tissue participating in and regulating endocrine and paracrine funtions[7]. The diversity of adipokines is directly linked to sympathetic excitation, metabolic regulation, including insulin sensitivity and appetite, inflammatory response and other homeostatic mechanisms. Some of the most prominent members of this family, as far as metabolic processes and cardiovascular function are examined, are: leptin, adiponectin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and tumor necrosis factor alpha (TNF-α)[1,7]. Leptin levels are elevated in obese subjects, along with TNF-α, IL-6 and PAI-1 that are proatherogenic and prodiabetic, in contrast to plasma adiponectin that protects against vascular damage and metabolic syndrome and is reduced, as it would be expected[8]. The variety in cytokine profile, along with the anatomic and cellular diversity that differentiate SCAT and VAT clarify and support the physiological and metabolic properties excreted by each adipocyte group. VAT cells allow for increased insulin-mediated glucose uptake and are more insulin-resistant and lipolysis-prone that those of SCAT. In contrast, the latter, exhibit a greater capacity for postprandial free fatty acid and triglyceride uptake and storage[1]. Taking into consideration the pivotal role of VAT in metabolic impairment, as such is supported by its aforementioned properties, it is comprehensible that studying the metabolic properties of visceral adiposity and mainly, organ-specific depositions, such as epicardial fat, has been incremental in the process of stratification of cardiometabolic risk factors. In this review, we aim to compare the morphology of epicardial fat deposits between non-diabetic individuals and subjects with type 2 diabetes mellitus (T2DM). Moreover, we will discuss the affect excreted by the antidiabetic substances in epicardial VAT, while contemplating on its clinical utility, as estimated by means of cardiovascular risk reduction.

FUNCTION AND COMPOSITION OF EPICARDIAL FAT

Epicardial adipose tissue (EAT) is an adipocyte depot of VAT with anatomical continuity to the myocardial tissue, located under the visceral layer of the pericardium[9]. It has been suggested that it can serve as a quantifiable and modifiable therapeutic target for cardiovascular adverse events, as it can be measured with non-invasive imaging techniques such as two-dimensional echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI)[10]. Spatial imaging, as such is provided by MRI and CT scans, is preferable to that of two-dimensional echocardiography technique, in order to accurately measure the thickness of EAT. Along with technical shortcomings, operator- and subject- related variability deem echocardiographic imaging a formidable solution solely because of the rapid and cost-effective patient assessment it facilitates. Otherwise, MRI is considered to be the gold-standard method for EAT quantification and area placement, even though three dimensional image reconstruction by utilizing multidetector-row CT is slightly superior in achieving the latter[10,11].

On a cellular level, the epicardial adipocytes are embryologically derived from the splachnopleuric mesoderm, similarly to the mesenteric and omental adipocytes. EAT is characterized by high cellularity, defined by the concentration of adipocytes in this tissue being notably higher than that of other depots of adipose tissue[12]. EAT is a depot of white adipocytes, cells that specialize in energy storage, as opposed to brown adipocytes that are involved in energy expenditure[13].

EAT extends on an area exceeding 80% of the myocardial total surface in an otherwise healthy individual, spreading heterogeneously, mostly accumulating on the lateral and anterior walls of the right atrium[14]. The physiological structure and composition of EAT variates depending on age, gender, body weight and ethnicity[14]. The properties of EAT and its contribution in physiological and pathophysiological pathways have been extensively described. Due to its spatial distribution, EAT acts as a mechanical and thermoprotective layer for the myocardial tissue and coronary arteries. Through endocrine and paracrine function, epicardial adipocytes
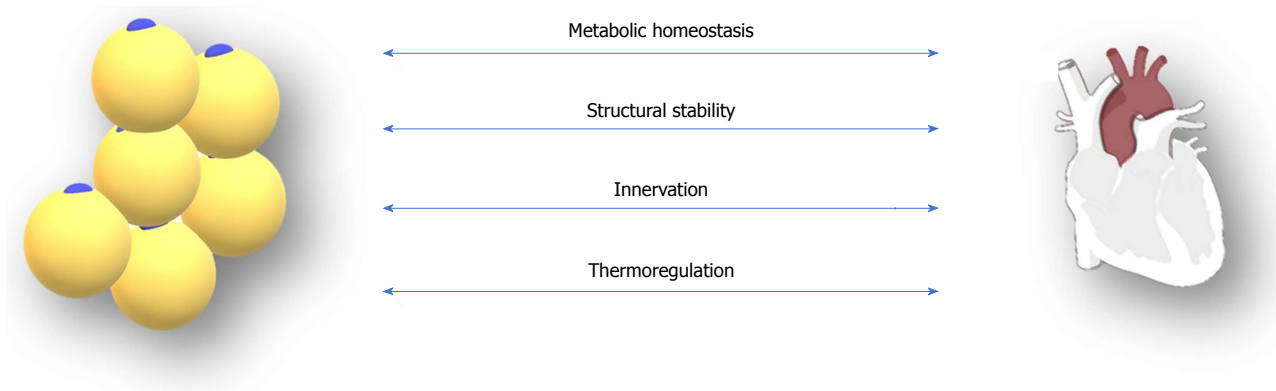
Figure 1 Mechanisms involved in the crossplay between the heart and the epicardial adipocytes.

ameliorate endothelial response of the coronaries and insulin sensitivity, while reducing oxidative stress of the cardiac tissue. Additionally, the small adipocytes of EAT are characterized by high rates of free fatty acids turnover, allowing for both energy supply and storage as demand shifts[14].

EPICARDIAL FAT, TYPE 2 DIABETES MELLITUS AND CORONARY ARTERY DISEASE

The prevalence of type 2 diabetes mellitus (T2DM) has quadrupled in the last three decades according to International Diabetes Federation (IDF) reports. The epidemic escalation has been attributed to numerous factors including population aging as a result of improved healthcare, socioeconomic development, unhealthy diet regimes and sedentary lifestyle[15].

EAT has been associated with numerous pathophysiological processes, such as coronary artery disease[16-18], even though the significance of such association has not been adequately supported by all relevant studies[19-20], electrophysiological abnormalities of the heart[21,22], cardiovascular disease in human immunodeficiency virus treated with antiretroviral therapy[23], amplified severity of non-alcoholic fatty liver disease[24,25], metabolic syndrome[26-29] and increased cardiovascular risk along with decline of renal function in individuals with T2DM[30-34].

The pathophysiological pathways linking T2DM and EAT, support a multifactorial causative relationship between EAT attributes and structure such as volume and endocrine function and cardiovascular disease severity in the diabetic individual.

EAT deposition can be associated with coronary vascular disease pathogenesis mainly by the dysregulation of cardiac metabolic processes and the disruption of the epicardial and myocardial structural integrity. Other mechanisms that could be involved in the interaction between EAT and coronary vasculature are nerve damage and impaired cryoprotection of the heart[35,36]. Furthermore, the epicardial adipocytes exhibit and arrhythmogenic potential, a theory suggested by many clinical trials ex-

ploring the causative relationship between EAT and atrial fibrillation[21] (Figure 1).

EPICARDIAL FAT AND ANTIDIABETIC DRUGS

Biguanides
Metformin is the most common first-line treatment choice for T2DM and a member of the biguanides drug class. Oral administration of the substance affects the liver and gut metabolic pathways in order for its hypoglycemic attributes to be put into effect[37]. Hepatic gluconeogenesis, glucose uptake, glycolysis and glucogen synthesis are some of the processes altered by metformin *via* AMP-activated protein kinase (AMPK)-dependent and -independent pathways[38].

At this point in time, there seem to be no randomized controlled trials designed for clarification of the effects excreted by metformin on the volume or function of EAT. Despite the fact that metformin has not been compared with placebo, as of yet, studies conducted on sitagliptin and liraglutide as add-on therapy to metformin monotherapy, combined with epicardial fat measurement, can be used as a preliminary source of data[39,40].

Results from these trials confirm the inferiority of metformin monotherapy when compared to metformin/sitagliptin and metformin/liraglutide for reduction of EAT volume. The findings can be either attributed to the synergy of two antidiabetic substances, affecting the EAT in a more effective manner than metformin alone, or to the complete lack of action of the biguanide class on the cardiac VAT deposits. The latter is supported by the results of the study performed by Iacobellis *et al*[40], that noted no EAT reduction in the metformin group during the 6-mo follow up period. Conversely, metformin has been previously shown to have positive effects on VAT, inducing its reduction on diabetic subjects[41]. Furthermore, studies have confirmed a metformin-induced increase of plasma omentin-1 levels, an adipokine produced by epicardial fat that ameliorates insulin sensitivity, inflammatory response and cardiovascular function[42]. Given the contradicting evidence concerning metformin, there is need for further research, as a definite conclusion on the manner by which biguanides interact with epicardial fat can only be provided

by a randomized controlled trial with EAT measurement.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (α-GIs) are a class of antidiabetic drugs acting in the epithelium of the small intestine mainly by delaying the digestion of carbohydrates through reversible and competitive inhibition of intestinal alpha-glucosidases, consequently reducing glucose absorption and attenuating postprandial hyperglycemia[43]. Some α-GIs are acarbose, miglitol and voglibose. Similarly to the biguanide class of antidiabetic medication, there is a lack of data concerning the administration of α-GIs and their effect on EAT mass, volume or metabolic activity.

Thiazolidinediones

Thiazolidinediones (TZDs), also known as glitazones, are peroxisome proliferator-activated receptor (PPAR) agonists with numerous actions, spanning from glycemic and lipid control to inflammatory signaling and cell cycle mediation[44]. The phenomenon of glitazone treatment and subsequent increase in body weight that has been supported by the results of numerous studies appears to be tissue-specific, since the VAT depot of the subjects remains unaffected while there is a shift of excess energy storage towards the SCAT[45-47].

Furthermore, pioglitazone treatment in T2DM or metabolic syndrome has been shown to attenuate the inflammatory signature of EAT by means of decreased expression of proinflammatory interleukins (IL) such as IL-1β, IL-1Ra and IL-10[48]. In addition to the positive effect on the metabolic profile of EAT, pioglitazone can affect the epicardial fat depot directly. Nagai *et al*[49] recruited 97 T2DM individuals that were divided into two groups according to baseline EAT thickness and underwent therapy with pioglitazone, along with EAT thickness measurement, at the beginning and after a nine-month follow-up period. Pioglitazone reduced the EAT thickness in both groups, with more prominent results in the subjects that had a greater EAT depot at baseline.

A different TZD, rosiglitazone, when administered to mice, induced the expression of brown adipose tissue-specific proteins by the EAT, a tissue type normally presenting having a hormonal profile consistent with that of white adipose tissue[50]. Brown adipose tissue has been linked to high rates of lipid turnover and reduced body weight, while it is essential for thermogenesis and homeostasis, in contrast to white adipose tissue that serves as an energy reservoir for the body[51].

The data derived from the studies examining the effect of glitazones and EAT correlates with the established theory that TZD-induced weight gain is not concurrent with VAT deposition. Moreover, TZDs appear to have a favorable effect on EAT both by regulation of endocrine functions and mass reduction.

Incretins

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that delays gastric motility, supresses appetite, stimulates glucose-dependent insulin and decreases glucagon secretion[52]. The enzyme dipeptidyl peptidase-4 (DPP-4) deactivates GLP-1 interrupting all incretin-stimulated signalling. DPP-4 inhibitors (DPP-4i) are one of the two categories of antidiabetic drugs acting on the incretin pathway, the other being GLP-1 receptor agonists (GLP-1 RA)[52]. DPP-4i inhibit both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) degradation, thereby increasing plasma concentrations and stimulating the pancreatic β-cell in order to better regulate glucose homeostasis.

DPP-4 inhibitors

The class of DPP-4is includes sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin[53]. Sitagliptin is the only DPP-4i whose effect on epicardial fat has been studied at this point in time. Lima-Martínez *et al*[39] formed a 24-wk interventional plan for 26 obese subjects with T2DM inadequately controlled on metformin monotherapy. Subjects meeting the inclusion criteria were introduced to a new regimen, receiving sitagliptin/metformin at a dosage of 50 mg/1000 mg respectively, twice a day. EAT deposits were reduced in size by approximately 15% (from 9.98 ± 2.63 to 8.10 ± 2.11 mm, P = 0.001) while the percentage of reduction in EAT was analogous to that of VAT (r = 0.456, P = 0.01).

While the aforementioned study establishes a favourable effect of sitagliptin on the mass of epicardial VAT, there is definite need for further research, in order to establish the reduction of EAT as a class effect of DPP-4is[39].

GLP-1 receptor agonists

GLP-1 RAs utilize the "incretin effect", similarly to DPP-4 inhibitors, so as to attenuate the diabetes-induced hyperglycemia. GLP-1 RAs are divided into short- and long-acting compounds that activate the GLP-1 receptor in a manner similar to that of the endogenous GLP-1[54]. Epicardial adipocytes have been shown to express GLP-1 and 2 receptor genes by use of RNA sequencing, while the possible quantity and dispersion pattern of the receptors in vivo has not been described[55]. Furthermore, GLP-1 and GLP-1 receptor signaling affect the differentiation and growth of adipocytes by regulation of fatty acid synthase activity[56]. Even though, the effects of numerous GLP-1 RAs have been studied in correlation to the metabolic regulation or mass reduction of visceral adipose tissue, the clinical trials concerning organ-specific deposits are few[40,57-60]. Current data on EAT remodeling by GLP-1 RAs is derived by two studies, conducted with liraglutide and exenatide[40,60].

A trial designed by Iacobellis *et al*[40] included 95 T2DM obese subjects with hemoglobin A1c $\leqslant$ 8% while being treated with metformin. The patients were randomized into two groups to either receive a combination of metformin/liraglutide, with the latter being administered once daily, in doses up to 1.8 mg, or stay on metformin monotherapy, up to 1000 mg administered twice daily

for 6 mo. EAT thickness measurements were acquired by ultrasound imaging at baseline and at 3 and 6 mo. Subjects in the liraglutide group presented with a decline in EAT thickness, 29% and 36% reduction from baseline at 3 and 6 mo respectively. Given that there were no similar changes in the metformin group, the EAT mass reduction is considered to be an effect of the liraglutide treatment, or possibly a result of the synergy between the two antidiabetic substances.

The study involving exenatide had a broader spectrum than that of liraglutide, examining the effect of the GLP-1RA on numerous VAT depots including epicardial, myocardial, hepatic and pancreatic adipose pads. Measurements of EAT thickness were performed by magnetic resonance imaging and spectroscopy at baseline and at 26 wk. A total of 44 obese individuals with uncontrolled T2DM, originally receiving oral therapy, were randomized to two groups, either receiving exenatide or other treatment chosen according to the local guidelines. EAT was reduced by approximately 8.8% after treatment with exenatide and by 1.2% on the patients receiving oral therapy, with the difference between the two being statistically significant ($P = 0.003$)[60].

Current research conducted on incretin treatment and ectopic adipose tissue deposition supports the theory that EAT reduction could be a class effect of GLP-1RAs and possibly a mediator of their beneficial actions on cardiovascular disease in the diabetic and obese subjects.

SGLT-2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic substances that bind on the SGLT2 transporter in the proximal tubule of the kidney, facilitating glucose excretion *via* hindering reabsorption. SGLT2-mediated reabsorption constitutes the main pathway by which the renal system maintains glucose homeostasis[61]. Administration of SGLT2 inhibitors in obese individuals with T2DM has been linked with abdominal VAT size reduction[62]. Additionally, the effects of SGLT2 inhibition on tissue-specific depots such as EAT have been clarified by studies performed on luseogliflozin, ipragliflozin, canagliflozin and dapagliflozin[63-67].

EAT measurements following a 12-wk period of luseogliflozin administration demonstrate that treatment with luseogliflozin can reduce EAT volume in combination with adipocyte-related inflammation and metabolic dysregulation on type 2 diabetic patients. Along with EAT, numerous parameters were modified after luseogliflozin therapy including body weight, fasting plasma glucose, insulin resistance and C-reactive protein (CRP) levels. A positive correlation was established between CRP and EAT reduction (r = 0.493, $P = 0.019$), suggesting a concurrent effect of the SGLT2 inhibitor on both the adipose tissue mass and metabolic activity[63].

Similar results concerning both EAT and biomarkers reduction were acquired after ipragliflozin administration, in a study designed similarly to that conducted for luseogliflozin. The two models differed in the selection

of the study population, with luseogliflozin treatment being applied to obese subjects while ipragliflozin was administered to non-obese T2DM individuals[64].

Yagi *et al*[65] studied the interaction of canagliflozin and EAT during a 6-mo period of treatment. The sample consisted of type 2 diabetic individuals, each of which was administered 100 mg of canagliflozin once daily. During the follow-up period EAT was evaluated by echocardiographic imaging while VAT and SCAT size fluctuation was monitored by use of impedance methods. The mean EAT thickness values were 9.3 mm and 7.3 mm at baseline and at 6 mo, respectively, with the change observed being statistically significant ($P < 0.001$) while there was only a trend for VAT and SCAT reduction.

Dapagliflozin and epicardial adiposity were examined through two different clinical trials, studying both the shift in metabolic activity and size of the adipocytes after treatment[66,67]. The metabolic profile of adipocytes promoted by dapagliflozin was assessed *ex vivo* on fat explants obtained from patients undergoing cardiac surgery on a trial designed by Díaz-Rodríguez *et al*[66]. Glucose uptake, transporter expression and adipokine secretion patterns were altered as a result of dapagliflozin application, a change indicative of a positive metabolic reform of the tissue induced by SGLT2 inhibition. Simultaneously, Sato *et al*[67] followed a more conventional approach, estimating the dapagliflozin-induced EAT volume reduction, by means of computed tomography imaging. Individuals receiving both dapagliflozin and other regimens for T2DM control were observed for 6 mo, with biomarker and EAT measurement at baseline and following completion of the study. While the two groups had similar EAT size measurement before the initiation of dapagliflozin therapy, the patients receiving the SGLT2 inhibitor presented with a greater reduction of epicardial VAT volume after treatment (-16.4 ± 8.3 for the dapagliflozin *vs* 4.7 ± 8.8 cm³ for the control group, $P = 0.01$), combined with lowered plasma levels of inflammatory adipokines.

Numerous studies conducted on many members of the SGLT2 inhibitor class of antidiabetic substances support the conclusion that EAT undergoes a multifaceted remodelling after SGLT2 inhibition, a trend that could be considered a class effect. The interconnection established between SGLT2 inhibitors and a known factor of cardiovascular risk such as epicardial adiposity could elucidate the manner by which the members of this class are cardioprotective, while, providing grounds for further therapeutic targeting of EAT (Table 1).

CONCLUSION

Epicardial adipose tissue exhibits a unique metabolic and pathophysiologic profile, as a result of its anatomical location and its cellular composition, rendering it an appealing therapeutic target for reducing cardiovascular risk and enabling endocrine homeostasis in the dysmetabolic individual. The recent studies concerning the effect of the antidiabetic substances on the multifactorial

Table 1 Antidiabetic drug and their effect on epicardial adipose tissue

Antidiabetic drug	Effect on epicardial adipose tissue
Biguanides	No effect/Possible synergistic effect with DPP-4 and/or GLP-1[39, 40]
Alpha-Glucosidase Inhibitors	Lack of data concerning the effect of this class
Thiazolidinediones	Decreased inflammatory cytokine release and thickness of EAT (pioglitazone) modulation of cellular hormonal profile (rosiglitazone)[49, 50]
Dipeptidyl peptidase-4 inhibitors	Reduction of EAT thickness (sitagliptin)[39]
Glucagon-like peptide-1 receptor agonists	Reduction of EAT thickness (liraglutide and exenatide)[40, 60]
Sodium-glucose cotransporter 2 inhibitors	Reduction of EAT thickness (luseogliflozin, ipragliflozin, canagliflozin, dapagliflozin) and inflammation (luseogliflozin, ipragliflozin, dapagliflozin)[63-67]

cardiomyopathy of the diabetic patient and, by extension, on epicardial adiposity, have yielded interesting results that support the use of treatment for a targeted approach, in order to reduce the size and metabolic activity of ectopic adipose tissue clusters. Despite the capacity of certain treatment regimens, mostly newer agents like GLP-1 agonists and SGLT-2 inhibitors, in the manipulation of both structural and functional parameters of the epicardial adipose tissue, the clinical efficacy of this approach remains unsubstantiated for the time being. There is definite need for further research, in order to elucidate whether the targeting of epicardial adiposity facilitates the procurement of better outcomes for individuals with diabetes and cardiovascular disease, while, additionally, clarify the manner by which the antidiabetic substances can attain such results.

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