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HEALTH SCIENCES

Drug-induced metabolic alterations in adipose tissue - with an emphasis in epicardial adipose tissue

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Abstract: Currently, research on understanding adipose tissue (AT) metabolism has increased significantly. AT is an endocrine organ, that releases proteins, specific metabolites, hormones, micro-RNAs and signaling lipids, all involved in a network of inter-organ communication. Among other effects, AT dysfunction contributes to a proinflammatory and diabetogenic state, from an early stage in the disease development. Overweight and obesity have reached epidemic proportions worldwide, which has been linked to the development and progression of high-comorbidity and diseases, such as insulin resistance, type 2 diabetes mellitus, hypertension, and cardiovascular diseases (CVD). Therefore, therapeutic strategies have been devised to modulate the composition of fat stores, including changes in lifestyle and/or pharmacological treatment for weight management or attenuation of cardiometabolic risk factors. As a result, life expectancy has been increasing. However, the population is being overmedicated and secondary adverse effects due to drug usage can be serious. Commonly prescribed drugs for immunosuppression and psychiatric disorders, such as severe depression and anxiety, are known to alter metabolism, particularly, in AT depots. In this review, we discuss important molecular mechanisms in AT, especially in epicardial AT (EAT), that are highly modulated by these drugs, and put forth EAT as a potential therapeutic target for CVD.

Key words: epicardial adipose tissue, pharmacological drugs, metabolic modulation, cardiometabolic risk factors

INTRODUCTION

In the last 20 years, research focusing on adipose tissue (AT) metabolism has increased significantly. However, understanding pharmacological drug-induced metabolic modulation of AT needs to be further advanced. AT is an endocrine organ that releases metabolites, lipids, and proteins, which are highly involved in networks of inter-organ cross communication (Scherer 2019). These important bioactive factors perform important functions, both locally and systemically. They can impact AT distribution, insulin sensitivity and secretion, energy expenditure, inflammation, blood pressure, metabolic homeostasis, as well as endothelial function (Blüher 2012). Therefore, AT dysfunction contributes to a proinflammatory, atherogenic, and diabetogenic state, which is mechanistically linked to the development of obesity-related cardiometabolic diseases (Blüher 2013).

Heart failure (HF) is a growing public health problem worldwide (Brown et al. 2017). The Global Burden of Disease Study 2017 has shown how that the total number of deaths from cardiovascular disease (CVD) has risen steadily since 1990 driven by ageing and population growth (GBD 2018). Epidemiological and clinical

data from the last decades indicated that the HF incidence and prevalence have also increased in patients with diabetes mellitus (DM), with increased risk directly associated with the severity of hyperglycemia (Lehrke & Marx 2017). In addition, overweight or obesity in the general population increase the risk of atherogenesis and myocardial infarction, which enables the development of chronic cardiac pathologies, regardless of the patient's diabetic status (Halade & Kain 2018).

DM is one of the most common chronic diseases in the present time, and it is not limited by either socioeconomic status or national boundaries (IDF 2019). DM is associated with the metabolic syndrome (MS), which is characterized by a combination of interrelated cardiometabolic risk factors such as abdominal obesity, insulin resistance, atherogenic dyslipidemia, hypertension, hyperuricemia and a pro-thrombotic, as well as a proinflammatory status (Luna-Luna et al. 2015). Ectopic fat deposition in important organs, such as muscle and liver, is a characteristic of the MS (Luna-Luna et al. 2015). In turn, this leads to nonalcoholic fatty liver disease (NAFLD) development and the increased thickness of the epicardial fat depot around the heart. Increased epicardial fat mass may lead to endothelial dysfunction of the coronary arteries, due to the proinflammatory phenotype and the imbalance between the cardioprotective and the harmful adipokines, lipids and other molecules secreted by this tissue, which may actively contribute to the increased risk of coronary atherosclerosis associated with MS (Luna-Luna et al. 2015, Iacobellis 2015).

DM can be classified into the following major categories: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes mellitus (GDM) and specific types of diabetes due to other causes, e. g., diseases of the exocrine pancreas (cystic fibrosis) and/or drug-induced diabetes (e. g., immunosuppressive agent used after organ transplantation) (ADA 2019). DM has increased worldwide and currently about 463 million people suffer from this disease, which carries a great severe socio-economic impact (IDF 2019). Furthermore, the DM prevalence, in 2045, is expected to rise to 700 million in adults, corresponding to an increase of 51% in 25 years (IDF 2019).

With the increasing incidence of obesity, T2DM and related complications, pharmacological drugs are being prescribed, and this may be linked to improvements in cardiovascular function (González et al. 2017). However, some drugs (e.g., immunosuppressive therapy, anxiety/depression drugs) have significant side effects and can interfere with glycemic control, thereby causing a diabetic state, further aggravating by the presence of micro and/or macrovascular complications. Therefore, it is of the utmost importance to study and evaluate the effects of pharmacological drugs used to reduce some of the cardiovascular risk factors, as well as immunosuppressive and antipsychotic drugs in human physiology. There are *in vivo* animal studies where some of these drugs have already been studied (Albaugh et al. 2011, Lopes et al. 2013, 2014a, b), typically human biopsies, such as muscle and fat (Pereira et al. 2012, 2013, 2014, García-Casarrubios et al. 2016, Díaz-Rodríguez et al. 2018, Sarsenbayeva et al. 2019), are also being collected for *ex vivo* analyses, to evaluate metabolic and energetic parameters, including their effects on insulin action and mitochondrial oxidative phosphorylation. However, more epidemiological studies are highly needed in order to understand how whole-body systemic modulation of physiology and metabolism is impacted by intake of these pharmacological drugs.

This review discusses some of the metabolic alterations caused by drugs mentioned above

used in clinical practice and highlights the need for further studies about the cardiometabolic effects of these drugs on specific tissues, such as epicardial adipose tissue (EAT), a promising target to attenuate CVD, which directly influences the constitution of the muscular wall of the heart and its vessels.

HUMAN ADIPOSE TISSUE: MORPHOLOGY AND PHYSIOPATHOLOGY

In 2016, the World Health Organization (WHO) estimated that nearly 2 billion adults were overweight and, of these, more than half a billion were obese (WHO 2018). Obesity, a serious threat to global health, is associated with the development and progression of diseases such as DM and subsequent micro and/or macrovascular complications (González et al. 2017). In the past, AT was considered an inert and static organ, functioning only as a storehouse of triglycerides (TGs). However, this idea is no longer correct. Currently, the adipocyte gained a new status among the scientific community. As shown in Table I, AT presents many roles that greatly exceed the energy reserve function (Ahima 2006, Boumelhem et al. 2017, Kumari et al. 2018, Luna-Luna et al. 2015, Poloni et al. 2015, Vielma et al. 2013, Zhao et al. 2018, Scherer 2019). Contrary to popular belief, AT is not composed by a single cell type, namely adipocytes. AT consists of a rich, complex, and coordinated conjunction of various cell types (Lenz et al. 2020). AT consists of mature and developing adipocytes, as well as a rich stromal vascular fraction (SVF) comprising fibroblasts, immune cells, mesenchymal stem cells (MSCs), pericytes, endothelial cells and pre-adipocytes (adipocyte progenitors) (Boumelhem et al. 2017), which highlights the extreme complexity and dynamics of this tissue (Lenz et al. 2020).

Different AT types have been described according to their body location, metabolic, energetic, and endocrine functions. White adipose tissue (WAT) is the predominant type of AT in mammals (Ahima 2006). This type of tissue is subdivided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Major subcutaneous WAT includes abdominal (superficial and deep) and gluteal-femoral depots (Kwok et al. 2016). VAT surrounds internal organs and can be sub-divided into intraperitoneal [omental (OAT) (around the stomach and spleen), mesenteric (around the intestines) and epiplastic (near the colon)], retroperitoneal (surrounding the kidneys), gonadal (adhering to the uterus/ovaries or epididymis/testis), as well as pericardial (PAT) and EAT (surrounding the heart) (Ahima 2006, Boumelhem et al. 2017, González et al. 2017, Kwok et al. 2016, Iacobellis 2015). Lenz et al. (2020) compared the cell type composition of four human adipose tissue depots (SAT, OAT, PAT, EAT) and concluded that SAT has the highest percentage of adipocytes, while EAT and PAT have many more immune cells compared to OAT and SAT, this finding can contribute to the understanding of each AT depots and their relations with metabolic health and disease (Lenz et al. 2020). In this review, the focus is EAT due to its important relation with the heart. While EAT is the fat depot immediately adjacent to the heart, PAT is the outer fat depot of the heart (Iacobellis 2015). Therefore, in recent years EAT has been described as exerting several essential roles in cardiovascular function.

Brown adipose tissue (BAT) regulates thermogenesis, mainly due to the presence of mitochondrial "Uncoupling Protein-1" (UCP-1). UCP-1 decouples mitochondrial respiration, dissipating chemical energy in the form of heat (Boumelhem et al. 2017, González et al. 2017, Kwok et al. 2016). BAT is usually located in the suprarenal, paravertebral and supraclavicular

Table I. Main roles of the adipose tissue (AT).

MAIN ROLES OF THE ADIPOSE TISSUE	REFERENCES
Energy metabolism: energy homeostasis	Luna-Luna et al. (2015), Boumelhem et al. (2017), Scherer (2019)
Lipid metabolism	Ahima (2006), Boumelhem et al. (2017)
Glucose metabolism	Ahima (2006), Boumelhem et al. (2017)
Thermoregulation: body temperature control	Luna-Luna et al. (2015), Boumelhem et al. (2017)
Signaling: interaction with neural/sympathetic (e.g., adrenergic) or hormonal (e.g., insulin) stimuli	Ahima (2006), Luna-Luna et al. (2015), Poloni et al. 2015)
Inflammation: secretes anti- (e.g., adiponectin) and proinflammatory (e.g., tumor necrosis factor (TNF), interleukin-6 (IL-6), leptin, resistin) adipokines	Ahima (2006), Poloni et al. 2015), Scherer (2019)
Regulation of immunometabolism	Vielma et al. (2013), Kumari et al. (2018), Zhao et al. (2018)

regions, as well as in areas near to large vessels (González et al. 2017). Finally, the third type of AT is presented as an adipose tissue with intermediate characteristics between WAT and BAT, thus presenting particularities of both tissues (González et al. 2017). In this type of AT, adipocytes are called beige or brite. The genesis of these adipocytes is thought to be in multipotent pre-adipocytes found in various WAT deposits (González et al. 2017). However, it is also hypothesized that these beige adipocytes come from the trans-differentiation of white adipocytes into beige adipocytes, a process called WAT browning (Boumelhem et al. 2017, González et al. 2017, Kwok et al. 2016, Sidossis et al. 2015). Beige adipose tissue is mainly located in the inguinal and neck regions, in order to function as adaptive thermogenesis (González et al. 2017). Given the morphological, genetic, protein and metabolic points of view, brown and beige adipose tissues are different from WAT; actually, differences in cell size, lipid droplets appearance, UCP-1 expression, mitochondrial content, and respiration, as well as metabolism are noticeable (Kwok et al. 2016, Sidossis et al. 2015). For treatment of metabolic complications associated with obesity in humans, the ability of UCP-1-positive adipocytes to uncouple mitochondrial oxidative phosphorylation and dissipate energy in the form of heat may be a very promising strategy (Sidossis et al. 2015). Thus, activation of the human BAT may have significant implications for health (Sidossis et al. 2015).

Furthermore, adipose-derived stem cells (ADSCs), that are MSCs found in the SVF of AT, play critical roles in obesity, adipose inflammation, and metabolic disorders (Zhao et al. 2018). MSCs have been recognized as producers of exosomes (Zhao et al. 2018). Exosomes are the nanosized

(30–100 nm) extracellular vesicles, which are secreted by a donor cell and are internalized into an acceptor cell, thus, playing a critical role in intercellular crosstalk and cellular regulation (Mittelbrunn & Sánchez-Madrid 2012, Zhao et al. 2018). Exosomes carry various biological molecules, including mRNAs, microRNAs (miRNAs), proteins, cytokines, and lipids, and, therefore, plays a pivotal role in the exchange of genetic information between cells (Mittelbrunn & Sánchez-Madrid 2012, Sahoo & Emanueli 2016, Zhao et al. 2018). Increasing evidence suggests that the molecules within exosomes vary with cell types and environmental conditions, and the recipient cells respond to exosome uptake with expressional and functional changes (Sahoo & Emanueli 2016). In fact, obese mice treated with ADSC-derived exosomes from lean mice exhibited reduced WAT inflammation, improved metabolic homeostasis, and resistance to obesity progression (Zhao et al. 2018). However, the direct impact of exosomes in the immune system remains to be investigated (Zhao et al. 2018). Recent evidence has also suggested that mature adipocytes together with certain immune cells directly regulate the activation and proliferation of adipose immune cells (Huh et al. 2014).

Approximately 90% of the lipid content in the adipocyte is composed of TGs (Thompson et al. 2010). In the post-prandial state, and with the rise in insulin levels, blood glucose and lipids are stored as TGs in adipocytes (Goldberg et al. 2008, Nye et al. 2008). On the other hand, in the fasted/pre-prandial state or when energy expenditure increases, for example, during exercise, AT provides energy via TGs hydrolysis, providing glycerol and free fatty acids (FFA) to the body, a process known as lipolysis (Schweiger et al. 2006, Thompson et al. 2010).

When the TGs accumulation capacity in SAT is exceeded – low expandability (dysfunctional SAT), the remaining TGs can spill over into other tissues, which are not adapted to the accumulation of the extra fat. Therefore, ectopic fat deposition occurs in other insulin-sensitive tissue, such as, liver and muscle (Luna-Luna et al. 2015). This can interfere with tissue physiology, and insulin sensitivity, leading to the appearance of pathophysiological tissue conditions. Furthermore, increased visceral adiposity is significantly linked to long-term changes in different cardiac structures, and in several forms of heart diseases, such as hypertensive and diabetic cardiomyopathies (González et al. 2017).

EPICARDIAL ADIPOSE TISSUE AND ITS METABOLIC IMPLICATIONS

EAT is located between the myocardium and the visceral layer of the pericardium, with no muscle fascia separating the two tissues (Iacobellis 2015). Thus, EAT surrounds heart muscle and coronary arteries, and shares with these organs the same microcirculation (coronary arteries) and to modulate their tissue-dependent functions under either normal physiological or pathological conditions (Vacca et al. 2016, Iacobellis & Mahabadi 2019a, Luna-Luna et al. 2015). Histologically, EAT is composed of a variety of different cell types that maintain homeostasis, and can also modulate systemic functions. EAT is composed by small white and beige adipocytes and pre-adipocytes, but, also, stromovascular and immune cells, ganglia and interconnecting nerves (Iacobellis & Mahabadi 2019b). Metabolically, it is thought that EAT protects the heart against elevated levels of circulating FFA since it has great capacity for fatty acid uptake and incorporation (Iacobellis & Barbaro 2008, Luna-Luna et al. 2015, Aldiss et al. 2016), likely functioning as a metabolic buffer

in the heart niche. Pezeshkian et al. (2009) have describe EAT as a local and rich myocardium-specific TGs depot (Pezeshkian et al. 2009). In addition to the high rate of lipogenesis, the rate of FFA release in EAT was reported to be greater than that of others fat depots, such as perirenal fat in adult guinea pigs (Marchington et al. 1989, Pezeshkian et al. 2009, Aldiss et al. 2016). The rich fatty acid composition of EAT (saturated fatty acids) is hypothesized to be crucial to the full and proper development of myocardial functions (Marchington & Pond 1990, Pezeshkian et al. 2009), since about 50 to 70% of the energy to maintain cardiac contractile function depends on the β-oxidation of long chain fatty acids (Lopaschuk et al. 2010). EAT is a type of visceral WAT with a phenotype typically similar with BAT and beige adipose tissue, in particular due to its high levels of UCP-1, as described previously (Sacks et al. 2009, 2013, Cherian et al. 2012, Aldiss et al. 2016). Specifically, EAT highly expresses BAT-specific genes, such as homologous domain-containing protein-16 (PRDM-16), peroxisome proliferator-activated gamma coactivator 1-alpha receptor (PGC-1α) and UCP-1, when compared to other BAT deposits (Luna-Luna et al. 2015). Therefore, EAT is involved in myocardial thermoregulation and is essential for maintaining the temperature of this vital organ.

However, under obesity and diabetes states, EAT becomes thicker and dysfunctional, promoting cardiovascular damage (Cherian et al. 2012, Iacobellis & Barbaro 2008). EAT appears to be increased simultaneously with the other VAT deposits and it also correlate with higher body mass index (BMI) levels (≥30 kg/m^2) and higher WAT/BAT ratio (Cherian et al. 2012, González et al. 2017, Iacobellis 2015, Luna-Luna et al. 2015). The overload of fatty acids in patients with both diabetes and obesity is followed by an increase in β-oxidation, which may lead to excessive production of reactive oxygen species (ROS) in cardiac mitochondria (Matloch et al. 2016). Some studies suggest that in patients with HF, EAT suffers more oxidative stress than SAT does (Iacobellis 2016, Matloch et al. 2016, McAninch et al. 2015, Patel et al. 2017), which underscores the central role of EAT in the development of heart diseases. Thus, increased amounts of EAT may in part contribute to left ventricular hypertrophy, leading to alterations in left ventricular function, diastolic dysfunction and attenuated septal wall thickening (Matloch et al. 2016, Iacobellis & Barbaro 2019). EAT can be seen as an active cardiac endocrine organ that produces both pro- and anti-inflammatory adipokines (Iacobellis & Barbaro 2019). The imbalance in the levels of these autocrine, paracrine and vasocrine secreted adipokines may contribute to the modulation of major atherogenic pathways (Cherian et al. 2012, Iacobellis & Barbaro 2019), contributing to an aggravation of heart disease, with systemic consequences. EAT has a unique transcriptome and secretome when compared to SAT (Gaborit et al. 2017, Lenz et al. 2020). It has been described that the expression of the inflammatory transcriptome in EAT is upregulated in the presence of advanced coronary artery disease (CAD), the most common type of CVD that is usually caused by atherosclerosis, and DM (Camarena et al. 2017, Iacobellis 2015). Increased production of proinflammatory factors by EAT may impact systemic insulin resistance in patients undergoing cardiac surgery (Matloch et al. 2016, Patel et al. 2017). Therefore, there is a clear relationship between EAT thickness, insulin resistance and CAD (Díaz-Rodríguez et al. 2018).

Insulin regulates glucose and lipid levels, protein expression and energy homeostasis, predominantly in liver, skeletal muscle, and AT (Boucher et al. 2014). This process begins with the binding of insulin to its receptor (IR

– insulin receptor) on the cell surface, activating its intrinsic tyrosine kinase by promoting the autophosphorylation of tyrosine residues (Boucher et al. 2014). IR activation triggers various signaling pathways, and one of the most well-known and important metabolic pathways involves the phosphatidylinositol 3-kinase (PI3K), 3-phosphoinositide-dependent protein kinase 1 (PDK-1) and Protein Kinase B (PKB, Akt) (Boucher et al. 2014). PI3K-PDK-1-Akt mediate many of insulin's intracellular effects, namely, glucose transport, lipid synthesis, gluconeogenesis, and glycogen synthesis (Boucher et al. 2014). Positive and negative modulators, such as mammalian target of rapamycin complex 2 (mTORC2) - required for full activation of Akt - and protein phosphatases 2B (PP2B, also known as calcineurin) - that has been shown to dephosphorylate Akt, respectively, act in this signaling pathway ensuring adequate and coordinated biological responses to insulin in different tissues and under diverse physiological conditions or pathological states (Boucher et al. 2014). However, the insulin signal can be disrupted and may result in insulin resistance an important underlying cause for T2DM development (Yang et al. 2004, Jansson et al. 2003).

Our previous results demonstrated that insulin-stimulated glucose uptake and isoproterenol-stimulated lipolysis are some of the metabolic processes that are significantly distinct in epicardial compared to sternal subcutaneous isolated adipocytes from patients with cardiac diseases, with indication for elective open-heart surgery. Glucose uptake and isoproterenol-stimulated lipolysis are significantly decreased in EAT when comparing with SAT (Burgeiro et al. 2016). In addition, the adipocyte size is smaller in EAT compared with SAT (Burgeiro et al. 2016).

Furthermore, we have shown that the endoplasmic reticulum (ER) stress was increased in EAT from patients with cardiac disorders compared to paired sternal SAT biopsies (Burgeiro et al. 2018). This ER overactivation might increase autophagy and may have a protective/survival function, since it promotes the degradation of dysfunctional proteins, thus contributing to a better adaptation of the myocardium to adverse conditions. ER stress-mediated cell death is not active in this unique type of VAT; however, EAT shows an increased tendency for apoptosis (Burgeiro et al. 2018).

The causes of insulin resistance are numerous, and the mechanisms are multifactorial. In rare cases, the origin is genetic, but in most cases, insulin resistance can be triggered by dysfunction at the molecular and cellular levels. Insulin action disruption can be caused by lipotoxicity, inflammation, hyperglycemia, mitochondrial deregulation, and ER stress, which interfere with gene expression through alterations in inhibitor and/or activator proteins resulting in a deregulation of insulin action (Boucher et al. 2014, Burgeiro et al. 2016, 2018). ER stress has been observed in human AT under numerous pathological conditions, such as in EAT from HF patients, indicating that ER stress may play a crucial role in AT disorders, including T2DM and obesity (Burgeiro et al. 2018, Gregor et al. 2009). Similarly, regulation of autophagy-related genes is activated in AT of obese patients and is linked with AT dysfunction (Maixner et al. 2016). Under physiological states, quality control mechanisms are involved in the maintenance of protein homeostasis (proteostasis); however, if ER stress is excessive, apoptosis can be induced (Burgeiro et al. 2018).

Moreover, mitochondrial dysfunction may contribute to insulin resistance and T2DM (Brown et al. 2017, Xiao et al. 2014), since adipocytes need functional mitochondria to generate the

required ATP for the synthesis and secretion of adipokines, lipogenesis, lipolysis (Xiao et al. 2014) and other AT-related functions. Our preliminary data have also shown significant changes in mitochondrial dynamics and increased oxidative stress in EAT compared to SAT in these patients (Burgeiro et al., unpublished data). This could be a result of an elevated inflammatory status in this tissue, impacting the myocardium.

Until recently, the paracrine effect of EAT on the myocardium was thought to be mediated through either protective adipokines, including adiponectin, adrenomedullin, and omentin, or proinflammatory adipokines such as, angiotensinogen, tumor necrosis factor (TNF), interleukin-6 (IL-6) and visfatin, leading to endothelial and smooth muscle cell proliferation, atherogenesis, and destabilization of atherosclerotic plaque (Patel et al. 2017). However, with the exosome-mediated genetic exchange between the donor and the recipient cell, new attention regarding dynamic intercellular communications between EAT and other tissues has been apparent (Patel et al. 2017). Curiously, adipocytes have recently been identified as major sources of circulating miRNAs, mostly via exosomal release, thereby, adding a further level of complexity to the regulatory control executed by these fat cells (Brown et al. 2017, Patel et al. 2017, Thomou et al. 2017). miRNAs are small, noncoding RNAs (containing about 21 nucleotides) which are involved in the posttranscriptional regulation of gene expression (Thomou et al. 2017). Thus, adipose-derived exosomal miRNAs constitute a novel class of important signaling molecules that AT can secrete, regulating metabolism (Thomou et al. 2017).

Obesity and DM can change the profile of miRNAs in circulation (Nunez et al. 2017, Pek et al. 2016, Tian et al. 2015). Recently, a specific miRNA matrix was uncovered in EAT from CAD patients (Vacca et al. 2016). Compared with controls, the expression patterns of 15 miRNAs appeared significantly upregulated, including miR-135b-3p (a direct target of inflammatory pathways), while 14 miRNAs were downregulated, such as, miR-455-3p (a potential role in accelerating brown adipocyte differentiation) and miR-193b-3p (promoting adiponectin secretion in human adipocytes) (Vacca et al. 2016). They found a downregulation of AT-related metabolic pathways, in EAT of CAD patients, as a consequence of a suppressed transcriptional activity of lipid-sensing nuclear receptors (e.g. retinoid X receptor alpha, RXRa) and other transcription factors which are involved in the regulation of metabolism (e.g. Forkhead box protein O1, FOXO1; sterol regulatory element-binding protein 1, SREBP-1) (Vacca et al. 2016). Suppression of most represented genes in the pathway analysis in EAT of CAD patients pointed to an intriguing downregulation of genes involved in lipid metabolism and mitochondrial function (e.g. Lipoprotein lipase, LPL; Phosphatase and tensin homolog, PTEN) (Vacca et al. 2016).

Since the heart is an organ with permanent and rhythmic contractile activity, which unlike skeletal striated muscle, cardiac muscle needs a constant source of energy. This energetic cardiac source is, at least in part, provided by epicardial adipocytes that provide fuels in the form of lipids and other metabolites, including adipokines and other immune-modulating factors. Due to its typical and a unique organ-specific location, EAT has been mostly studied using imaging (Dey et al. 2012, Demircelik et al. 2014, Iacobellis 2015). Although there are some molecular and metabolic studies in EAT, its molecular phenotype and cellular fitness under physiological and pathological conditions and its crosstalk with myocardium is largely unknown. Therefore, assessing its physiopathology and molecular biology regarding its crosstalk with the

myocardium and the neighbouring vasculature, as well as metabolic effects in particular due to pharmacological drug use, is crucial.

PRESCRIPTION DRUGS – MODERN LIFE – BENEFICIAL OR HARMFUL SIDE EFFECTS

Life expectancy has been increasing, largely due to modern medicine. In fact, more medications are being prescribed today than previously (Garber & Brownlee 2019, Gallagher et al. 2020). Pharmacological drugs are being prescribed to treat most of the existing diseases. Not surprisingly, worldwide, the population is overmedicated (with prescription or over-the-counter), with the non-negligible risks of adverse drug reactions that this entails (Brahma et al. 2013, Fincke et al. 1998, Qato et al. 2016).

Many patients benefit from taking multiple drugs for weight loss (e.g., phentermine + topiramate) and treatment of cardiometabolic risk factors, such as dyslipidemia (e. g., atorvastatin), T2DM (e. g., metformin, sitagliptin, exenatide, liraglutide, dapagliflozin, pioglitazone), hypertension (e.g., Olmesartan Medoxomil + Hydrochlorothiazide), because they provide durable efficacy and are mostly well tolerated (González et al. 2017, Lundkvist et al. 2017, Parisi et al. 2019, Tokubuchi et al. 2017, Xourgia et al. 2018, Distel et al. 2012, Nagai et al 2008, Gomes et al. 2008). Naturally, people who have more than one chronic disease need to resort to polypharmacy (Garber & Brownlee 2019, Gallagher et al. 2020).

Immunosuppressive therapies, such as glucocorticoids, calcineurin inhibitors and inhibitors of the mammalian target of rapamycin (mTOR) are for instance drug classes that are being prescribed for immune disorders or after organ transplantation throughout the life of the transplanted patient (Coutinho & Chapman 2011, Pereira et al. 2013, 2014). Depression and psychiatric disorders are also currently treated with phamacologic strategies, some of the most prescribed drugs are Olanzapine and Aripiprazole (Riedel et al. 2010).

In spite of being life-saving and the benefit/risk ratio may outweigh possible adverse effects, many of these drugs increase a person's risk of suffering a serious, sometimes life-threatening side effect. Some of these drugs have been more studied than others in regard to their side effects. Some of them greatly modulate metabolism, in particular in EAT and others visceral adipose tissue, including alterations in volume/thickness and phenotype (González et al. 2017, Xourgia et al. 2018). Immunosuppressive drugs can cause metabolic dysfunction that ultimately can lead to insulin resistance, hypertension, T2DM and CVD (Coutinho & Chapman 2011). Figure 1 offers an overview of possible drug-induced metabolic alterations, detrimental or beneficial effects, for some of the major prescribed drug classes (e.g., immunosuppressive drugs, antipsychotic drugs; drugs to reduce cardiovascular risk) discussed in this review. Some of the evidence for these underlying mechanisms involved in the related side effects, are reviewed below. Studies unravelling the *in vivo* or *ex vivo* metabolic effects of these drugs in the various insulin sensitive tissues are scarce although drug-induced metabolic dysfunction should be an important research topic.

DRUGS COMMONLY PRESCRIBED

Immunosuppressive agents

Organ transplantation is a surgical intervention that is used when all other health recovery options are exhausted. High mortality remains the greatest threat to the success of solid organ transplantation, despite improvements in the control of post-transplant immunological

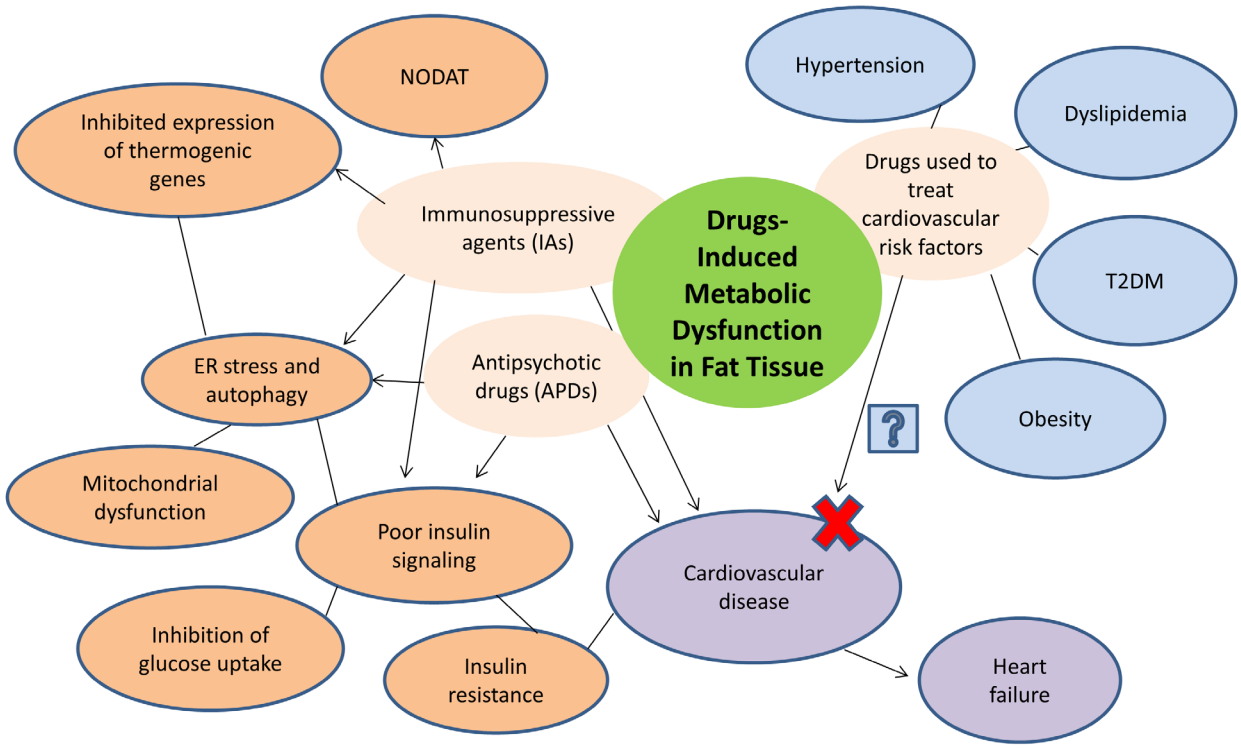

Figure 1. Drugs- Induced Metabolic Alterations: A Complex Web. Immunosuppressive agents and antipsychotic drugs can cause metabolic dysfunction in adipose tissue that, ultimately, can lead to cardiovascular disease and, consequently, heart failure. Many of the drugs used to treat cardiovascular disease, are also known for their significant and undesirable side effects. ER: endoplasmic reticulum. NODAT: New-onset diabetes mellitus after transplantation. T2DM: type 2 diabetes.

reactions, with major improvements in graft survival (Alebiosu & Ayodele 2005). Worldwide, in 2017, 139.024 solid organ transplants were performed, an increase of 7,25% compared to 2015. Of these cardiac transplants were 7.881, an increase of 12,2% compared to 2015 (GODT 2019).

Therefore, it is essential to prevent the rejection of transplanted organs. Efforts in this regard have been made for years and the therapy with immunosuppressive agents (IAs) is one of the medical approaches with most efficient results, since the first IAs were used in 1949 (Allison 2000). However, one of the most worrying side effects related to the IAs usage after transplantation is the development of cardiovascular and metabolic complications. This may include impairment of glucose tolerance and insulin secretion, hypertension, as well as an increase in circulating lipids, which can lead to a diagnosis of New-onset diabetes mellitus after transplantation (NODAT) (Lopes et al. 2013, 2014 a, b, Pereira et al. 2012, 2013, 2014).

Importantly, NODAT occurs in up to 50% of transplant recipients and is one of the major adverse effects of IAs treatment (Buchanan 2009). Moreover, NODAT increases the risk of organ rejection in the long-term and death of the patient receiving the organ (Montori et al. 2002). The most commonly used IAs are glucocorticoids (Coutinho & Chapman 2011) and calcineurin inhibitors (Pereira et al. 2014), which include cyclosporin A (CsA) and tacrolimus (Tac). Others also available are known as antiproliferative agents, for example inhibitors of the mammalian target of rapamycin (mTOR), including sirolimus (SRL) also known as rapamycin – (RAPA) (Pereira

et al. 2013). Immunosuppressive therapies, such as RAPA treatment, have both beneficial and detrimental effects on glucose, glycogen, and lipid metabolism of both human and rodents, particularly detrimental to WAT (Lopes et al. 2013, 2014a, b, Pereira et al. 2012, 2013). RAPA may be an alternative to calcineurin inhibitors after transplantation due to its antiproliferative and immunosuppressive properties, and, consequently, due to its antitumor and/or antiatherogenic activity, as well as increased safety against renal toxicity (Subramanian & Trence 2007). However, these therapies contribute to the development of NODAT, in part through the disruption of the insulin signal, causing a significant decrease in the insulin-stimulated glucose uptake into adipocytes (Pereira et al. 2013, 2014, Fonseca et al. 2018).

García-Casarrubios et al. (2016) have reported that, just like in white adipocytes, brown adipocytes are also RAPA targets, leading to a decrease in insulin signaling, inhibition of glucose uptake, lipolysis, and reduction of the expression of thermogenic genes, as well as alteration in mitochondrial bioenergetics (García-Casarrubios et al. 2016). Although distinct mechanisms appear to be involved in the RAPA effects on BAT and WAT, the results strongly suggest that BAT dysfunction could also be a major contributor to the development of NODAT, but the RAPA direct effects on EAT are still unknown.

RAPA usage has been associated with a reduced risk of acute rejection when administered in conjunction with CsA (Kahan 2000). However, glucocorticoids and CsA appear to be the main agents that affect glucose homeostasis after solid organ transplantation (Subramanian & Trence 2007, Pereira et al. 2014). RAPA appears to be more associated with dyslipidemia and less with NODAT (Lopes et al. 2013, 2014a, b, Pereira et al. 2012, 2013). Thus, when therapy involves the administration of RAPA and/or calcineurin inhibitors, there is an increased risk of developing metabolic disorders.

Several studies have shown that RAPA impairs mitochondrial function, in several tissues, including cardiac tissue (myocardium) reducing mitochondrial oxygen consumption (Albawardi et al. 2015), and inducing mitochondrial dependent apoptosis in pancreatic beta-cells (Constantinescu et al. 2016). Mitochondrial dysfunction in EAT may be in part due to excessive calcium release from the ER because of the altered function of this organelle, leading to ER stress (Burgeiro et al. 2018, Fonseca et al. 2014). To enhance this stress, mammalian cells possess a homeostatic set of important protein signaling pathways and transcription factors involved in the unfolded protein response (UPR) (Burgeiro et al. 2018, Fonseca et al. 2015). There is some controversy between the effect of increased autophagy by RAPA and the induction or attenuation of ER stress (Fonseca et al. 2015, Jung & Choi et al. 2016, Song et al. 2016). Importantly, since mTOR regulates the expression of many miRNAs, RAPA can also exert its effects through the alteration of miRNA expression in different types of cells (Totary-Jain et al. 2013, Zhang et al. 2016). For instance, RAPA regulates the cardiac expression of the diabetic marker miRNA miR-29 (Arnold et al. 2014). However, the effects of IAs on mitochondrial function, miRNA expression or the expression of thermogenic genes in EAT are unknown.

Antipsychotic drugs

Life expectancy for patients suffering from depression, bipolar disorder, schizophrenia, or other mental disorders is greatly reduced compared to the general population (Skrede et al. 2012, Sarsenbayeva et al. 2019). Treatment with certain antipsychotic drugs (APDs), such

as Olanzapine or Aripiprazole, are well known for their potential serious metabolic adverse effects, including obesity, dyslipidemia, T2DM, hypertension, which are all established CVD risk factors (Skrede et al. 2012, Sarsenbayeva et al. 2019). Studies indicate that dyslipidemia could occur independently of weight gain (Skrede et al. 2012). The majority of metabolic studies that have been performed are on rodent models, in order to understand the metabolic side effects of these two drugs, on glucose and lipid metabolism in relevant peripheral tissues (Skrede et al. 2012). Many studies have identify AT as one of the main organs to be affected by APDs (Victoriano et al. 2010, Albaugh et al. 2011, Skrede et al. 2012, Gall et al. 2013, Li et al. 2019, Zhang et al. 2014). This may explain, in part, some of the side effects observed, such as, induced weight-independent elevation of serum TGs, together with upregulation of several genes involved in lipid biosynthesis. These findings support the existence of tissue-specific but in part weight-independent direct effects of these drugs on energy metabolism, via as yet uncharted mechanisms (Skrede et al. 2012, Sarsenbayeva et al. 2019). Therefore, a better understanding of antipsychotic-induced metabolic dysfunctions to prevent or treat efficiently the related adverse effects in AT, especially in the EAT, is needed. To our knowledge, there is no information on the effects of antipsychotic drugs on EAT. Due to its relationship with the heart and heart disease, it is extremely important to know the effects of these drugs on this tissue. Olanzapine, for example, can reduce lipolysis of adipocytes under acute treatment in therapeutic concentrations (Sarsenbayeva et al. 2019). And at supra-therapeutic concentrations, APDs can alter the expression of genes involved in the regulation of mitochondrial functions in adipocytes (Sarsenbayeva et al. 2019). This could potentially contribute to adverse metabolic effects regarding the crosstalk between EAT and the myocardium. Studies have revealed cardiac consequences, such as sudden cardiac death, due to the use of antipsychotic drugs among individuals with psychiatric disorders (Zhu et al. 2019). Further research about antipsychotic drugs-associated adverse cardiac/metabolic effect will need to be performed, to prevent the devastating cardiac outcomes, mainly in elderly people affected with dementia and long-term therapies (Gareri et al. 2014). Few data exist in the literature on this topic.

Common drugs to treat cardiovascular risk

Interestingly, some of the most efficient therapies strategies (nutritional changes, moderate aerobic physical activity) against the development of cardiometabolic pathologies and/or in order to ameliorate potential cardiovascular abnormalities in obese and T2DM patients may target the altered composition and distribution of fat stores (e.g. modulate visceral and epicardial fat volumes and phenotypes) (González et al. 2017). Besides nutritional changes and physical activity recommendations to prevent and combat cardiovascular diseases, several pharmacological drugs are being prescribed as well. In recent years, the administration of statins (simvastatin and atorvastatin) and antidiabetics drugs [such as peroxisome proliferator-activated receptor gamma (PPARγ) agonists – known as thiazolidinediones (glitazones), biguanides (such as metformin), sodium-glucose cotransporter 2 (SGLT2) inhibitors (e. g. dapagliflozin), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (such as liraglutide and exenatide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (e. g. sitagliptin)], has increased. And a marked reduction in plasma cholesterol and TGs, together with an increase HDL-cholesterol levels in obese individuals has been observed (González et al. 2017, Parisi et al. 2019, Xourgia et al. 2018). However, weight loss

may not be achieved in all patients, and fatty liver, inflammation, and thrombosis may not be improved (González et al. 2017). Thus, combined therapies can be beneficial through synergistic actions, while decreasing adverse effects and increasing tolerability (González et al. 2017).

To note that drugs that promote the expansion or inflammation of epicardial adipocytes may lead to cardiac disorders (such as insulin and sulfonylureas), whereas treatments that reduce the proinflammatory characteristics of epicardial adipocytes may diminish the HF risk (such as statins, SGLT2 inhibitors and thiazolidinediones) (Grosso et al. 2014, Packer 2018, Parisi et al. 2019, Sato et al. 2018). Díaz-Rodríguez et al. (2018) evaluated the effects of dapagliflozin, a SGLT2 inhibitor, on human EAT and found that dapagliflozin increased glucose uptake, reduced proinflammatory chemokines secretion (with a beneficial effect on endothelial cell human coronary artery), and improved differentiation of EAT cells (Díaz-Rodríguez et al. 2018). Pioglitazone, simvastatin or combined treatment, in patients with CAD and MS substantially reduced EAT volume and inflammatory plasmatic markers (Grosso et al. 2014).

Moreover, incretin-based therapies, one of the most recent therapeutic options for T2DM treatment, can modify various elements of that disease, including increase glucose-dependent insulin exocytosis (Godinho et al. 2015). In addition, activation of glucagon-like peptide-1 receptors (GLP-1R) results in other long-term effects besides the stimulation of insulin biosynthesis, including increased β-cell proliferation and promotion of resistance to apoptosis (Godinho et al. 2015, Hausenloy & Yellon 2012, Saraiva & Sposito 2014). GLP-1 reduces plasma glucose by inhibiting the pancreatic secretion of glucagon, which in turn reduces hepatic gluconeogenesis (Saraiva & Sposito 2014). DPP-4 inhibitors increase GLP-1 availability and correct the "incretin defect" observed in T2DM patients (Furuhashi et al. 2015, Godinho et al. 2015). Recent studies have been focused on other cytoprotective effects of the GLP-1R agonists or DPP-4 inhibitors on other organs/tissues that are involved in serious T2DM complications, including the heart, kidney, and retina (Cantini et al. 2016, Godinho et al. 2015). Increased cardiac output, deceleration of gastric emptying and inhibition of food intake are some of these effects (Furuhashi et al. 2015, Godinho et al. 2015, Saraiva & Sposito 2014).

More significant, GLP-1R agonists or DPP-4 inhibitors could reduce the obesogenic phenotype of WAT and encourage its trans-differentiation to BAT, either in VAT and EAT depots, leading to cardiovascular protection (Godinho et al. 2015, González et al. 2017). Moreover, studies in obese rodents revealed that the GLP-1R agonist (such as liraglutide and exenatide) induced WAT browning and prompted plasma clearance of TGs and glucose, following BAT activation (thermogenesis) (Beiroa et al. 2014, López et al. 2014). Furthermore, in obese mice, sitagliptin (DPP-4 inhibitor) enhanced energy expenditure by UCP-1 upregulation in BAT repositories (Shimasaki et al. 2013). Remarkably, it has been recently discovered that human EAT expressed the GLP-1R gene, which supports the hypothesis of a beneficial direct effect of GLP-1R agonists on epicardial adipocytes that surround the heart (Iacobellis et al. 2017a). Although there are no known studies on the molecular mechanisms of GLP-1R agonists in EAT, Dozio et al. (2019) found in their recent study that expression of GLP-1R in EAT is directly correlated with genes promoting beta-oxidation and white-to-brown adipocyte trans-differentiation (Dozio et al. 2019). Therefore, GLP-1 analogs may target EAT GLP-1R and therefore reduce local adipogenesis, improving lipid utilization and inducing white-to-brown fat trans-differentiation (Dozio et al. 2019). However, the molecular mechanism behind the effect of DPP-4 inhibitors on EAT are still poorly understood and more studies are urgently need.

Thus, the incretin system may represent a safe candidate for improving adipose deposition and distribution, and subsequent cardiovascular injuries, in obese and T2DM patients, although their molecular mechanisms are not fully understood (Dutour et al. 2016, Lima-Martínez et al. 2016, Marso et al. 2016, Iacobellis et al. 2017b).

CONCLUSIONS AND PERSPECTIVES

Adipose tissue, including epicardial fat, can change from its protective status to being pathological in obesity and T2DM, becoming dysfunctional and releasing fatty acids and proinflammatory factors by disrupting cardiovascular homeostasis. In this regard, some non-pharmacological interventions (lifestyle changes, such as: diet alterations, caloric restriction and physical exercise), as well as pharmacological interventions have shown promising results at the systemic level, particularly sustained reductions in body weight, glycaemic control and blood pressure management, with a significant reduction in EAT thickness, anti-inflammatory properties, change in energy balance from obesogenesis to thermogenesis, and subsequently improvement of cardiovascular lesions.

Nevertheless, further studies are needed to evaluate the metabolic effects of drugs in certain cells and tissues, especially in the EAT depot. To the best of our knowledge, there are no other studies in the scientific literature that have assessed cardiometabolic effects of antidiabetic drugs, such as incretin-mimetics, on epicardial adipocytes, despite the beneficial role of these drugs in controlling T2DM and obesity. It is also unknown the adverse metabolic effects of immunosuppressive and antipsychotic medications in EAT. Thus, EAT may serve as a target for these pharmacological agents used in the treatment of T2DM, obesity, dyslipidemia, immunosuppression, schizophrenia and may induce beneficial or harmful cardiovascular and metabolic effects. Figure 2 shows probable metabolic effects of drugs on EAT. Table II summarizes the pharmacological classes most discussed in this study and their main beneficial and/or detrimental effects on EAT cells or in other depots of AT.

Furthermore, it is worth mentioning that research using EAT explants has limitations including tissue availability and the lack of healthy control. Moreover, many patients are not naive to medication often when tissues are being collected for studies. In fact, patients with cardiac diseases are under medication to control some of the cardiovascular risk factors mentioned before. On the other hand, although cell lines and animal models can be useful tools, they suffer from the disadvantage that they might not reflect the structure, morphology, immunology and function of human AT physiology. In addition, EAT is a very different fat depot compared to the fat depots that researchers have been studying for years, such as subcutaneous or omental adipose tissues. Unlike other depots, EAT is hardly present in rodents, and, therefore, hard to access and study, except in higher mammals, particularly in humans.

Therefore, it is essential to gain knowledge of the molecular mechanisms by which drugs induce metabolic dysfunction in AT, in particular in EAT, to prevent the cardiovascular disease risk and mortality associated with pharmacological therapies, as well as to better inform on combination therapy for diabetic patients. Since drug-induced metabolic diseases are poorly studied, much more is needed so that new drugs can be developed to replace older ones, to avoid severe side effects and metabolic dysfunction.

Table II. Pharmacological classes most discussed in this study and their main effects in isolated adipocytes or adipose tissue depots.

DRUG-TYPES			Main effects in isolated adipocytes or adipose tissue depots	REFERENCES
Immunosuppressive agents (IAs)	Calcineurin inhibitors	Cyclosporin A (CsA)	- Impairs glucose tolerance and increases lipolysis of both human and rodent adipocytes - Increases adipocyte weight and diameter - Removes GLUT4 from the cell surface of differentiated human adipocytes via an increased rate of endocytosis	Lopes et al. 2013, Lopes et al. 2014a, Pereira et al. 2013, Pereira et al. 2014
		Tacrolimus (Tac)	- Increases lipolysis and inhibits lipid storage in isolated human adipocytes and/or adipose tissue - Removes GLUT4 from the cell surface of differentiated human adipocytes via an increased rate of endocytosis	Pereira et al. 2013, Pereira et al. 2014
	Rapamycin (RAPA) = Sirolimus (SRL)		- Impairs glucose tolerance and increases lipolysis in human adipocytes or in isolated rodent adipocytes in WAT - Reduces the phosphorylation and/or protein levels of the insulin signaling proteins of both human and rodent adipocytes - Inhibits lipolysis, alters mitochondrial bioenergetics and reduces thermogenesis in BAT of the rats	Lopes el at. 2013, Lopes et al. 2014a, Lopes et al. 2014b, Pereira et al. 2012, Pereira et al. 2013, García-Casarrubios E et al. 2016
Antipsychotic drugs (ASDs)	Olanzapine		- Upregulates several genes involved in lipid biosynthesis in adipose tissues and decreases lipolytic activity on rat adipocyte - Induces low grade inflammatory state in adipose tissue of the rodent models - Reduces BAT thermogenesis in female rats	Skrede et al. 2012, Albaugh et al. 2011, Victoriano et al. 2010, Li et al. 2019, Zhang et al. 2014
	Aripiprazole		- Decreases triglyceride content of adipose tissue, increases multivacuolar cell presence, increase the pre-adipocytes proliferation in rats	Skrede et al. 2012, Gall et al. 2013

Drugs used to treat cardiovascular risk factors	Statins		- Modulates thickness and inflammatory profile of human EAT (simvastatin and atorvastatin)	Grosso et al. 2014, Parisi et al. 2019
	Antidiabetics	Biguanides	- No effect/Possible synergistic effect with DPP-4 inhibitors and/or GLP-1RAs on human EAT - Positive effects on VAT, inducing its reduction on diabetic subjects through a possible mechanism of fatty acid oxidation (metformin)	Xourgia et al. 2018, Lima-Martínez et al. 2016, Iacobellis et al. 2017b, Tokubuchi et al. 2017
		Thiazolidinediones	- Decreases inflammatory cytokine release and thickness of human EAT (pioglitazone) - Induces a browning of the EAT of obese fatty Zucker rat that probably contributes to the increase in lipid turnover (rosiglitazone)	Grosso et al. 2014, Xourgia et al. 2018, Nagai et al. 2008, Distel et al. 2012
		GLP-1RAs	- Reduces human EAT thickness (liraglutide and exenatide)	Xourgia et al. 2018, Dutour et al 2016, Iacobellis et al. 2017b
		DPP-4 inhibitors	- Reduces human EAT thickness (sitagliptin) - UCP-1 up-regulation in *BAT* of the obese mice (sitagliptin)	Xourgia et al. 2018, Lima-Martínez et al. 2016, Shimasaki et al. 2013
		SGLT2 inhibitors	- Increases glucose uptake, reduced proinflammatory chemokines secretion and Improves differentiation of human EAT cells (dapagliflozin)	Xourgia et al. 2018, Díaz-Rodríguez et al. 2018, Sato et al. 2018

BAT, brown adipose tissue; DPP-4, dipeptidyl peptidase-4; EAT, epicardial adipose tissue; GLP-1RAs, glucagon like peptide-1 receptor agonists; GLUT4, glucose transporter type 4; SGLT2, sodium-glucose co-transporter 2; UCP-1, uncoupling protein 1; VAT, visceral adipose tissue; WAT, white adipose tissue.

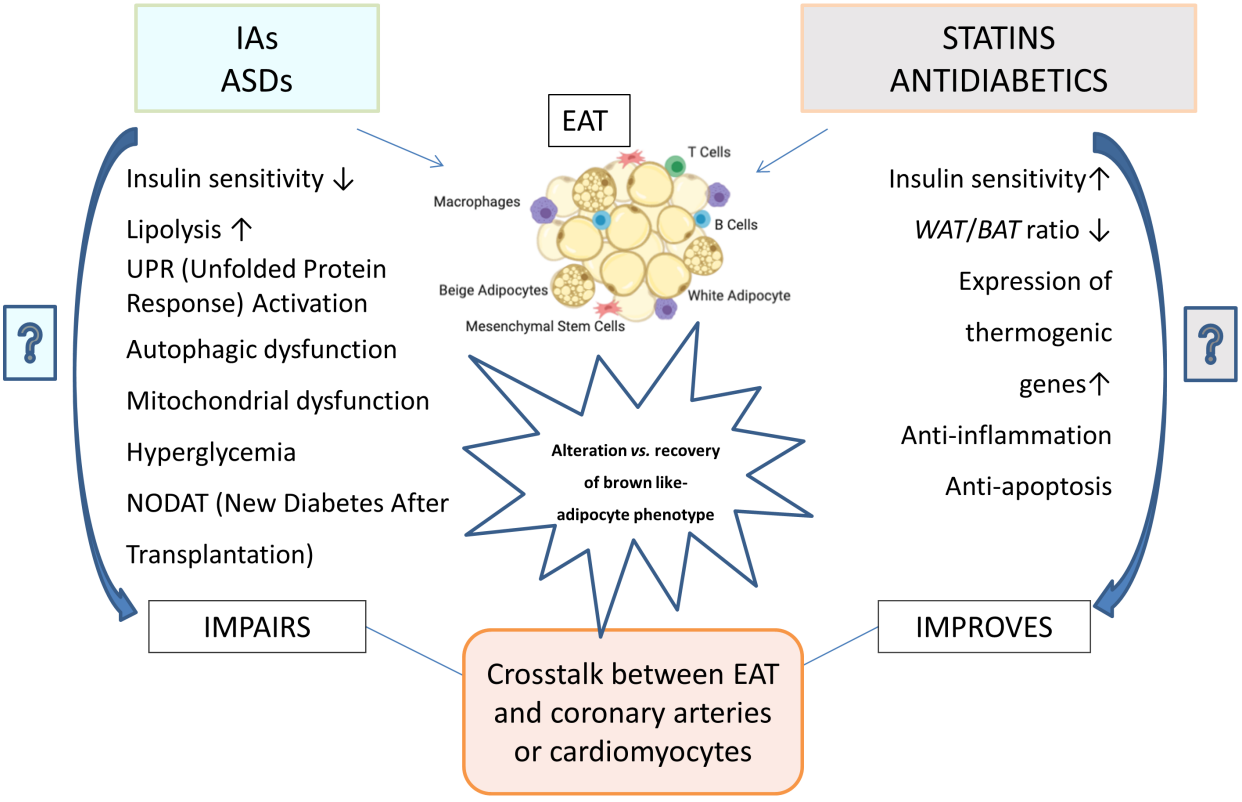

Figure 2. Probable metabolic effects of drugs on epicardial adipose tissue (EAT). Our hypothesis is that EAT may serve as a target for pharmacological agents. These may include immunosuppressive agents (IAs), antipsychotic drugs (APDs), statins, antidiabetic drugs, that are used in the treatment of T2DM, obesity, dyslipidemia, immunosuppression, schizophrenia and may induce beneficial or harmful cardiovascular and metabolic side effects. These pharmacological agents can improve (e.g., statins and antidiabetic drugs) or impairs (e.g., IAs and APDs) the crosstalk between EAT and cardiomyocytes or coronary arteries. APDs: antipsychotic drugs. BAT: brown adipose tissue. EAT: epicardial adipose tissue. IAs: immunosuppressive agents. NODAT: New-onset diabetes mellitus after transplantation. UPR: unfolded protein response. WAT: white adipose tissue. A part of figure was created with BioRender (Biorender.com).

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