Cardiovascular Diabetology

REVIEW

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SGLT2 inhibition and adipose tissue metabolism: current outlook and perspectives

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Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have emerged as important agents for the treatment of type 2 diabetes mellitus (T2DM). SGLT2 inhibitors have been associated with improved cardiovascular outcomes, not only through their immediate hemodynamic effects—such as glycosuria and (at least temporary) increased natriuresis—but also due to their multifaceted impact on metabolism. Recently, studies have also focused on the effects of SGLT2 inhibitors on adipose tissue. Aside from the well-documented effects on human adiposity, SGLT2i have shown, both in vitro and in murine models, the ability to reduce fat mass, upregulate genes related to browning of white adipose tissue, influence adipocyte size and fatty acid oxidation, and improve oxidative stress and overall metabolic health. In humans, even though data are still limited, recent evidence seems to confirm that the SGLT2i effects observed in cardiovascular outcome trials could be partially explained by their impact on adipose tissue. This review aims to clarify the impact of SGLT2i on adipose tissue, highlighting their role in metabolic health and their potential to transform treatment strategies for T2DM beyond glucose metabolism.

Introduction

SGLT2i are a class of medications originally employed in treatment of T2DM. Their mechanism of action and therapeutic impact extend beyond conventional glucose regulation through glycosuria, providing several benefits in cardiovascular (CV) [1–3] and kidney diseases [4]. Their immediate hemodynamic effects—resulting from glycosuria and (at least temporary) increased natriuresis—reduce intravascular volume and arterial pressure, helping to mitigate heart failure and improve kidney perfusion and function. Additionally, their cardiovascular benefits are supported by longer-term metabolic remodeling, which includes improved adipose tissue metabolism, enhanced insulin sensitivity, and reduced systemic inflammation [5, 6]. However, despite these observations, the precise mechanisms behind these benefits are not yet fully understood and are thus the focus of ongoing research with investigation into SGLT2 expression being extended beyond renal tissues. There are indications that SGLT2 are expressed (although at considerably lower levels) in other tissues such as the pancreas, liver, muscle, and adipose tissues, however, the functional relevance of SGLT2 in these non-renal tissues, remains to be fully elucidated [7].

In the DAPAHEART TRIAL, we enrolled patients with stable coronary artery disease with suboptimal glycemia, randomizing them in a 1:1 ratio to dapagliflozin or placebo for 4 weeks. We found a significant 30% increase in coronary flow reserve in the dapagliflozin group [8]. Moreover, compared to all the other visceral and subcutaneous adipose tissue (SAT) depots, we saw a reduction

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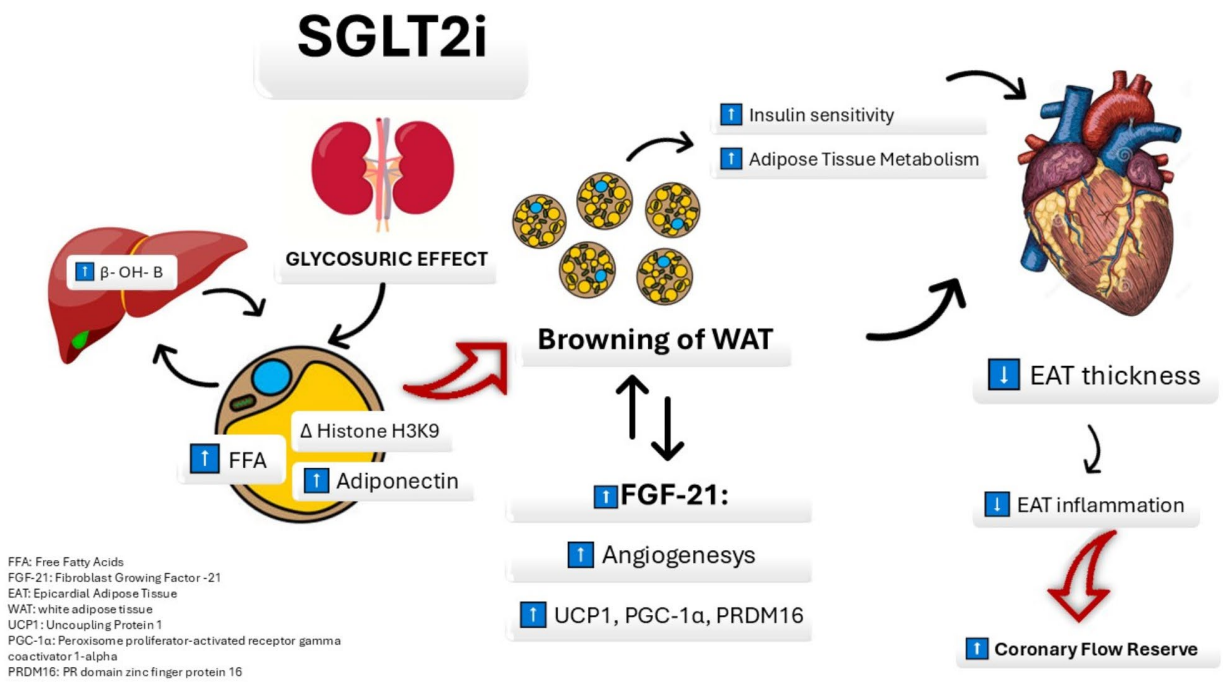
Graphical abstract



Keywords Diabetes, Metabolism, Adipose organ, SGLT-2i, Precision medicine, Epicardial adipose tissue

in the thickness of epicardial adipose tissue (EAT), associated with a reduction in glucose uptake [9]. We interpreted these results as a decrease in the pro-inflammatory state of EAT, a known risk factor for CV diseases, which justified the observed improvement in coronary flow reserve (CFR) [10]. In fact, the effects of SGLT2i on EAT inflammation has also been demonstrated in vitro and in rats, in which SGLT2i have been shown to increase the level of ketone bodies, thus reducing EAT inflammation and atrial dysfunction [11].

The role of adipose tissue in the pathogenesis of type 2 diabetes and cardiovascular diseases is well known [12] and the recent spurt in drugs that cause a significant reduction in adipose tissue together with a significant reduction in CV risk, has brought renewed attention [13–15]. Indeed, several drugs used in the management of T2DM have shown promising results in weight control [15]. In this context, SGLT2i seem to exhibit metabolic effects independently of the fluid contraction caused by glycosuria. Glycosuria reduces blood glucose levels and contributes to caloric loss [3], but there also seems to be a direct action of SGLT2i on adipose tissue metabolism, as evidenced, for example, by their impact on EAT [9]. Based on these premises, this review aims to examine and clarify the effects of SGLT2i on adipose tissue, focusing on their impact on metabolic health and evaluating how they might transform treatment strategies for type 2 diabetes and metabolic diseases.

SGLT2i: class effects and unmet needs

Several SGLTi, dapagliflozin, canagliflozin, empagliflozin and ertugliflozin, are currently approved in Europe [16]. The primary mechanism of action of SGLT2i involves the inhibition of the SGLT2 protein in the proximal convoluted tubule of kidney, which is responsible for the reabsorption of approximately 90% of filtered glucose. By blocking this transporter, SGLT2i promote glucosuria, leading to a reduction in glycemia [17]. Data from randomized clinical trials suggest that the beneficial effects observed can be ascribed to class features and are not specific to the single drug [18].

Beyond their glucose-lowering effects, SGLT2i have shown significant cardiorenal benefits, extensively validated in several landmark clinical trials, demonstrating that SGLT2i reduce the incidence of major adverse cardiovascular events (MACE), to a varying extent depending on the drug and/or the enrolled population. They significantly lower the risk of cardiovascular death and regardless of T2DM status reduce the risk of hospitalization for heart failure and slow the progression of kidney failure [18, 19]. Importantly, SGLT2i have been shown to enhance heart functional capacity, as indicated by

improvements in peak VO2 and performance in the 6-minute walking test (6MWT), both key metrics that reflect overall cardiovascular and metabolic health of patients. Beyond these physiological benefits, SGLT2i have also been linked to improved quality of life, reinforcing their role in comprehensive cardiometabolic care [20].

Blood pressure reduction, nephron remodeling, reduction in arterial stiffness, are all well-known mechanisms associated with the CV benefits observed with the use of SGLT2i [21] but they are not sufficient to fully explain the metabolic effects.

The impact of SGLT2i on adipose tissue, in terms of body weight loss and the shift in energy source from glucose to fat [22], has been observed in both rodents and humans. These findings suggest potential mechanisms that could explain cardiovascular (CV) benefits. However, the molecular and metabolic mechanisms underlying this interaction remain not fully understood.

We thus decided to focus on the impact of SGLT2 inhibition on adipose tissue and its direct or indirect potential effects on the cardiovascular system.

The plasticity of adipose tissue

Adipose tissue, which includes both white adipose tissue (WAT) and brown adipose tissue (BAT) forms a unitary true organ in both rodents and humans, challenging the conventional view of adipose tissues as independent functional structures [23]. Recent studies have demonstrated the continuity between various adipose depots in the body underscoring the concept of a unitary adipose organ, which exhibits significant plasticity, since, as seen in rodents, it adapts to physiological changes such as cold exposure, obesity, and lactation, due to its role as an "endocrine organ" [23, 24].

WAT is the most abundant adipose tissue in the human body, mainly functioning as an energy storage depot, accumulating lipids in the form of large unilocular fat droplets within adipocytes. The most important function of WAT is its ability to release high energy molecules (fatty acids) in the intervals between meals, allowing survival for up to 6–7 weeks of fasting [25]. WAT also has very important endocrine properties which control the main behaviors for human survival (i.e. food search and intake [26, 27]) and play crucial roles in other important aspects of metabolism, immunity and inflammation by secreting hormones known as adipokines [25].

BAT is primarily responsible for thermogenesis, a process by which energy is dissipated as heat: this is made possible by the presence of numerous small lipid droplets and a high number of big mitochondria, rich in cristae, that contain uncoupling protein 1 (UCP1). This protein is highly specific and uniquely expressed in these mitochondria [28]. UCP1 allows BAT to generate heat by uncoupling oxidative phosphorylation from ATP production, a process especially vital for thermoregulation in cold environments. BAT activity has a positive effect on glucose metabolism and also performs endocrine functions [23, 25, 29, 30].

As mentioned, the adipose organ has plastic properties and conversion of WAT into BAT, and vice versa, has been widely demonstrated both in rodents and in humans [23, 31–33]. This process, known as "browning" of WAT, is characterized by the transformation of energy-storing white adipocytes into energy-burning brown adipocytes, primarily by the enhancement of UCP1 expression and thermogenesis in adipose tissue. SGLT2i have been shown to influence this process by promoting the release of Fibroblast growth factor 21, a key regulator that drives the upregulation of UCP1 and facilitates the metabolic reprogramming of adipocytes toward a thermogenic phenotype [34]. Morphologically, this phenomenon is characterized by the presence of beige adipocytes, within the adipose tissue, which exhibit features that are intermediate between white and brown adipocytes [25, 35]. The browning of WAT increases the body's energy expenditure and has been linked to improved metabolic health [36, 37]. Cold exposure is the major inducer of browning both in mice and humans [38], but physical exercise [39–41], nutrients [42] and even some drugs also seem to play a role [43–47].

This distinction between white and brown adipose tissue highlights the plasticity of fat cells and their varying roles in energy metabolism and thermoregulation.

Fibroblast growth factor 21 (FGF-21), a part of the fibroblast growth factor family, has been identified as a crucial regulator in the differentiation of brown adipocytes and promotion of the "browning" of adipose tissue. FGF-21 is an important metabolic regulator that also affects glucose homeostasis, insulin sensitivity and ketogenesis. Studies in rodents have shown that BAT is not only a target for FGF-21 but also a significant source of systemic FGF-21: BAT expresses and releases FGF-21 in response to thermogenic activation, for example during cold exposure, indicating that BAT plays a role in the systemic regulation of FGF-21 [48]. This discovery supports the hypothesis that FGF-21 has a physiological role in thermogenesis and the thermogenic recruitment of white adipose tissue browning through an autocrine-paracrine axis highlighting the plasticity of the adipose organ and the interplay between the WAT and BAT.

The adipose organ is thus considered a true endocrine organ involved in the metabolic system and has become a target to curb and treat diseases [38, 49]. The great plasticity of adipose tissue, effortlessly shifting between energy storage and thermogenesis, consolidates its role as a key regulator of metabolism and a powerful target for therapy in cardiovascular and metabolic diseases.

The cross-talk between adipose tissue and the cardiovascular system

The complex functions of adipose tissue, recently recognized as an organ [23], make it a crucial regulator of health and diseases. WAT and BAT are found in both subcutaneous (below the skin) and visceral depots (in close contact with viscera). Several studies have outlined the different properties of these two depots, as visceral fat accumulation is associated with adverse metabolic outcomes [50–52].

Focusing on the cardiovascular system, the endocrine and paracrine effects of adipose tissue play a core role in its physiological and pathological functions, underlying the importance of exploring the crosstalk between them [53, 54]. In fact, adipose tissue may be protective or harmful, with quality instead of quantity, as the principal variable [53, 55].

The main visceral adipose tissue involved in the cardiovascular system is the epicardial adipose tissue (EAT). It has several characteristics that render it a unique adipose tissue depot: it is in direct contact with the myocardium, which implies that the two tissues share the same microcirculation, and it contains mainly brown fat, suggesting that it is a metabolically active fat depot [56]. Physiologically, the EAT exerts protective effects: it is a source of free fatty acids [57], it secretes cardioprotective adipokines with anti-inflammatory and anti-atherogenic properties [58], it contributes to myocardial redox homeostasis through EAT-derived miRNAs [59] and last, but not least, it provides a direct source of heat to the myocardium protecting it during unfavorable hemodynamic conditions such as ischemia or hypoxia [60, 61].

In pathological conditions, such as obesity and diabetes, the EAT brown fat-like activity decreases substantially and the proportion of brown adipocytes decreases in favor of white adipocytes [35], promoting inflammation with all the well-known inflammatory consequences and deleterious metabolic effects [62–66].

On the other hand, it has been shown that pro-inflammatory and oxidative stimuli in diseased vessels and/or the myocardium can modify adipose tissue biology, suggesting a bidirectional crosstalk between the adipose tissue and the cardiovascular system [67, 68].

Other visceral adipose tissue depots are also involved in the cardiovascular system, due to their systemic, protective or harmful effects. In fact, BAT, mainly expressed in the cervical-supraclavicular (most common), perirenal/adrenal, and paravertebral regions [69, 70], exerts protective effects on cardiometabolic health [71]. In 2021, Cohen et al. reported that individuals with active BAT had lower prevalences of cardiometabolic diseases, and the presence of BAT was independently correlated with lower odds of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure and hypertension [71]. On the other hand, when adipose tissue becomes dysfunctional, as in obesity, cardiometabolic risk increases [72].

For all the above-mentioned reasons, not only the EAT, but also the other visceral adipose tissue depots have now become therapeutical targets to curb or treat cardiometabolic diseases [49, 56, 73, 74]. Since our data suggest that in just 4 weeks of treatment with the SGLT2i dapagliflozin we can obtain a reduction in EAT thickness of 19%, which probably induces a 30% increase in coronary flow reserve [8, 9, 75], we will focus our attention on the direct or indirect effects of SGLT2i on the adipose organ.

How do SGLT2i influence the adipose organ and how can they enhance wat browning? In vitro and rodent data

Several studies have described the beneficial effects of SGLT2i on the adipose organ through different mechanisms. Studies in rodents have demonstrated that SGLT2i treatment increases the synthesis of the ketone 3-hydroxybutyrate, which modifies histone H3K9 expression in adipocytes, consequently upregulating adiponectin synthesis in adipocytes [76]. This effect has also been observed in humans, as demonstrated by clinical studies that highlight the increased production of 3-hydroxybutyrate following SGLT2i treatment, further supporting its role in metabolic reprogramming [77]. Adiponectin is one of the most abundant adipokines secreted by WAT and enhances insulin sensitivity [78–80]. Indeed, adiponectin induces the activation of M2 anti-inflammatory macrophages, an important source of catecholamine for the activation of WAT browning [81].

Additionally, in a female rat model of polycystic ovary syndrome (PCOS) and insulin resistance, Pruett et al. showed that the administration of the SGLT2i empagliflozin for 4 weeks, (compared to a control group), reduced fat mass, leading to morphological changes in adipose tissue, specifically an increase in the number of small and medium-sized adipocytes and a reduction in the number of large adipocytes [82], an indirect sign of browning [25]. In fact, they found an increased expression of genes involved in mitochondrial biogenesis and fatty acid oxidation (i.e., browning induction), such as PGC1α and NRF1in WAT and the mitochondrial antioxidant enzyme superoxide dismutase (SOD2) in SAT. This suggests that SGLT2 have the potential to improve mitochondrial function and reduce oxidative stress in WAT [82]. Although the authors did not observe a significant reduction in oxidative stress after 4 weeks of treatment, other studies have described this reduction in male murine models, in which SGLT2i reduced oxidative stress and, consequently, improved mitochondrial function, thus positively influencing insulin resistance [83–85].

Studies conducted on rodents and human cardiac tissue have demonstrated that canagliflozin reduces oxidative stress by enhancing mitochondrial function and decreasing production of reactive oxygen species (ROS). This effect contributes to improved cardiac function, particularly in conditions such as heart failure and diabetic cardiomyopathy [86].

Recently, a study by Di Vincenzo et al. has investigated the impact of the SGLT2i dapagliflozin on the expression of FGF-21, one of the main inducers of WAT browning [87]. The authors assessed the gene expression of FGF-21 in myocardial tissue of obese rodents at baseline and after a 4-week treatment, and found that dapagliflozin treatment increases FGF-21 gene expression and reduces triglyceride content in myocardial tissue, indirectly suggesting that dapagliflozin promotes a browning effect [88].

Beyond these effects, it seems that dapagliflozin can promote the browning of WAT through the regulation of angiogenesis in adipose tissue. In obese rodents, Xiang et al. described an increased expression of angiogenic factors promoting the formation of new blood vessels in WAT together with a significant increase in the expression of browning genes UCP1, PGC-1α and PRDM16 (PR domain-containing 16). In this way, SGLT2i improve oxygen and nutrient delivery to the adipocytes, facilitating their metabolic shift towards a more energy-consuming phenotype thus promoting the browning process [89].

To summarize these findings, SGLT2i act on adipose tissue primarily by enhancing fat burning, increasing 3-hydroxybutyrate levels, which modify histone H3K9 methylation and acetylation in adipocytes, leading to an increase in adiponectin synthesis. The increased adiponectin induces activation of M2 anti-inflammatory macrophages, which promotes WAT browning with a consequent positive metabolic impact. In addition, in vitro and in vivo murine models have demonstrated that SGLT2i reduce fat mass, influencing adipocyte size, and upregulating genes involved in mitochondrial biogenesis and fatty acid oxidation, suggesting potential improvement in mitochondrial function and reduced oxidative stress. Lastly, SGLT2i can indirectly influence WAT metabolism by increasing the expression of myocardial FGF-21, which promotes angiogenesis and upregulates genes associated with brown adipocyte characteristics, such as UCP1, PGC-1α, and PRDM16, shifting white adipose tissue from energy storage to energy dissipation thus confirming the positive metabolic effect of this class of drugs.

Effects of SGLT2i on human adipose tissue

The positive effects of SGLT2i on the adipose organ, observed in vitro and in rodent models, also seem to be present in humans with mechanisms that go beyond simple glucose excretion. Indeed, it seems that the chronic glycosuria caused by SGLT2 inhibition leads to an adaptive increase in energy intake [22]. It has been demonstrated that the observed weight loss in patients treated with the SGLT2i empagliflozin, for example, was consistently less pronounced than expected, based on the amount of urinary glucose excretion [22]. This discrepancy suggests an adaptive increase in caloric intake as a compensatory mechanism for the calories lost through glycosuria, implying that it is necessary to combine SGLT2i with caloric restriction for major weight loss [22].

These findings were later expanded by the discovery of parallels between SGLT2i treatment and fasting-mimicking diets, suggesting that SGLT2i mimic the fasting state not only by promoting glycosuria and consequently reducing insulin concentration, a potent inhibitor of lipolysis, but also by influencing free fatty acid (FFA) metabolism by prioritizing FFA as the primary energy source for oxidation. This shift to FFA oxidation leads to increased circulating ketone bodies, resulting in more oxygen-efficient energy production, suggesting possible beneficial effects on adipose tissue morphology and physiology (i.e. browning) as observed in rodents [78–80], and also in humans [90].

The shift to FFA oxidation as a primary energy source with SGLT2i treatment, as observed in rodent models [91], could play a pivotal role in reducing fat mass. Moreover, by prioritizing FFA as the primary source of oxidation, SGLT2i signal an increased need for glucose to the cell. This leads to a higher number of GLUT4 being translocated to the cell membrane of adipocytes, improving insulin sensitivity [92, 93].

Regarding the anti-inflammatory effect seen in vitro and in rodent models, Buttice et al. recently conducted a systematic review and meta-analysis focusing on the effect of SGLT2i on inflammatory markers, adipokine profiles and insulin sensitivity, and found that SGLT2i significantly improve levels of adiponectin, interleukin-6 (IL-6), and tumor necrosis factor receptor-1 (TNF-r1). Moreover, they found an improvement in the homeostatic model assessment of insulin resistance (HOMA-IR) although there were no significant changes in other inflammatory biomarkers such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1), or FGF-21 levels, as seen in vitro and in murine models [94].

Further, a significant body of research has highlighted the impact of SGLT2i on adipose tissue distribution. Systematic reviews and meta-analyses of randomized controlled trials in patients with T2DM have consistently shown that SGLT2i substantially reduce not only body weight and body mass index (BMI) but also waist circumference and visceral fat area. In a systematic review and meta-analysis of randomized controlled trials, Wang

X. et al., provide evidence that in patients with T2DM, SGLT-2 inhibitors significantly reduce, though to different extents, visceral adipose tissue, subcutaneous adipose tissue, and ectopic liver fat. However, the high heterogeneity of the studies included suggests caution in drawing conclusions [95]. Overall, SGLT2 inhibitors seem to have a more pronounced effect on VAT and EAT compared to SAT leading to a reduction of inflammation and oxidative stress, which is associated with better metabolic outcomes. (Table 1).

In humans, all the data suggest beneficial effects on the adipose organ even though direct evidence of browning of adipose tissue is still lacking.

Table 1 Different effects of SGLT2i on human visceral or subcutaneous adipose tissue (VAT/SAT) [96–106]

AUTHOR	SGLT2i	SAT reduction	VAT reduction
Ito et al. (Diabetes Care, 2017)	Ipragliflozin	**- 9.2%** Reduction of SFA **(Subcutaneous Fat Area)** of **26,1 cm²** in 24 weeks	**- 16.9%** Reduction of VFA **(Visceral Fat Area)** of **26,1 cm²** in 24 weeks
Bando et al. (Diabetology International, 2017)	Ipragliflozin	**- 3.23%** Reduction of SFA **(Subcutaneous Fat Area)** of **5.8 cm²** in 12 weeks	**+ 0.63% increase** Increase in VFA **(Visceral Fat Area)** of **1.4 cm²**, limited compared to the control group that saw an increase of **20.4 cm²** in 12 weeks
Eriksson et al. (Diabetologia, 2018)	Dapagliflozin	**- 7.55%** Reduction in abdominal fat volume of **0.29 l** in 12 weeks	**- 6.72%** Reduction in abdominal fat volume of **0.27 l** in 12 weeks
Koshizaka et al. (Diabetes, Obesity and Metabolism, 2019)	Ipragliflozin	**- 7.03%** Reduction of SFA **(Subcutaneous Fat Area)** of **6.7 cm²**	**- 12.06%** Reduction of VFA **(Visceral Fat Area)** of **11,3 cm²**
Latva-Rasku et al. (Diabetes Care, 2019)	Dapagliflozin	**- 5%** Reduction of **SAT volume** of 0.28 l in 8 weeks **(Subcutaneous Adipose Tissue)**	**- 9.21%** Reduction in **VAT volume** of 0.35 l in 8 weeks **(Visceral Adipose Tissue)**
Inoue et al. (Journal of Diabetes Investigation, 2019)	Ipragliflozin	**- 6.06%**	**- 9.73%**
McCrimmon et al. (Diabetologia, 2020)	Canagliflozin	*Not investigated*	**- 6.6%** Reduction in **visceral fat** of 0.1 kg
Han et al. (Journal of Clinical Medicine, 2020)	Ipragliflozin	*No significant differences detected*	**- 12.53%** Reduction of VFA **(Visceral Fat Area)** from 209.1 ± 63.3 cm^2 a 182.9 ± 63.7 cm^2
Brown et al. (European Heart Journal, 2020)	Dapagliflozin	**- 6.66%** Reduction of SAT volume **(Subcutaneous Adipose Tissue)**	**- 22.13 %** Reduction of VAT volume **(Visceral Adipose Tissue)**
Kinoshita et al. (Journal of Diabetes Investigation, 2020)	Dapagliflozin	*Not investigated*	**- 10.24%** Reduction of VFA **(Visceral Fat Area)** from 193.4 ± 10.9 cm^2 to 173.6 ± 9.1 cm^2 after 28 weeks
Gaborit et al. (Cardiovascular Diabetology, 2021)	Empagliflozin	*No significant differences detected*	**- 5.73%** Reduction **of visceral abdominal fat** from 211.2 ± 31.4 to 199.1 ± 38.7 cm^2 in 12 weeks

Are SGLT2i cardiovascular benefits mediated by their effect on the adipose organ?

Several reviews and meta-analyses have highlighted the significant benefits of SGLT2i on cardiovascular outcomes in patients with diabetes, showing reduced risks of all-cause mortality, hospitalization for heart failure, CV death, and the composite of hospitalization for heart failure or CV death, regardless of baseline diabetes status.

Several mechanisms have been proposed to explain the beneficial CV effects of SGLT2i, namely reduction of blood pressure and intravascular volume, and reduction of myocardial oxygen consumption, all of which can lead to a decreased workload on the heart and improved cardiac function [86, 107]. However, recent studies suggest that CV benefits may be linked, in part, to the effects of SGLT2i on insulin resistance, a necessary condition in the pathogenesis of T2DM [108]. Thus, since adipose tissue is a fundamental part of insulin resistance, the direct action of these drugs on this tissue cannot be neglected [109, 110]. Indeed, by improving insulin sensitivity and reducing insulin resistance, SGLT2i can indirectly impact the metabolic profile, further contributing to cardiovascular protection [5]. A series of recently published studies have highlighted the significance of the effect of SGLT2i on epicardial adipose tissue (EAT) reporting that SGLT2i treatment led to a significant reduction in EAT thickness (about 19%) [111–113], the main adipose tissue depot implicated in CV risk (Table 2). It is important to note that EAT volume is a more sensitive measure than EAT thickness, with imaging modalities such as MRI or CT providing greater sensitivity compared to ultrasound. Furthermore, volumetric assessments using Simpson's disc method are more accurate than those based on geometric assumptions. These advanced methodologies ensure a more precise evaluation of EAT, enhancing our understanding of its role in CV risk and the impact of SGLT2i therapeutic interventions [114].

Our group has also recently described a selective decrease in EAT glucose uptake (about 21.6%) in patients with T2DM and CAD after a 4-week treatment with dapagliflozin [9]. This could suggest that the selective reduction in EAT thickness and glucose uptake could be due to a decrease in EAT inflammation, which is a known risk factor for CV diseases [56, 73, 121–123]. We have previously described a 30% increase in myocardial flow reserve [8] and we speculate that SGLT-2i treatment, by restoring the anti-inflammatory properties of EAT, improves coronary microvascular dysfunction, leading to an amelioration of myocardial flow reserve [9]. We can also speculate that, dapagliflozin treatment longer than 4 weeks may be able to restore the brown feature of EAT [124].

The CV benefits of SGLT-2i can thus, in part, be ascribed to their effect on adipose tissue, even though further experiments are needed to confirm this.

Conclusion

In conclusion, SGLT2i have been shown to have a fundamental role in T2DM and weight control not only by facilitating glycosuria but also by effects mediated by

Table 2 Effect of SGLT2i on human epicardial adipose tissue (EAT) [9, 106, 112, 115–120]

AUTHOR	SGLT2i	EAT reduction
Yagi et al. (Diabetology & Metabolic Syndrome, 2017)	Canagliflozin	**- 21.5%** (Decreased **EAT thickness** from 9.3 ± 2.5 to 7.3 ± 2.0 mm)
Bouchi et al. (Cardiovascular Diabetology, 2017)	Luseogliflozin	**- 5.1%** (Decreased Epicardial Fat Volume EFV from 117 cm^3 to 111 cm^3 after 12 weeks)
Sato et al. (Cardiovascular Diabetology, 2018)	Dapagliflozin	**- 16.4%** (Decreased **EAT volume** from 115 ± 22 cm^3 to 98.6 ± 13.7 cm^3). Decrease of −16.4 ± 8.3 cm^3
Iacobellis et al. (Obesity, 2020)	Dapagliflozin	**- 15 %** reduction in **EAT thickness**: over 12 weeks **- 20%** over 24 weeks
Sato et al. (Journal of Atherosclerosis and Thrombosis, 2020)	Dapagliflozin	**- 13.45%** Decreased **EAT volume** from 113 ± 20 $cm^3$to 97.8 ± 17.2 cm^3 after 6 months of treatment. Decrease of -15.2 ± 12.8 cm^3
Requena-Ibáñez et al. (JACC Heart Failure, 2021)	Empagliflozin	**- 10.14%** (5.14 ml reduction in **EAT volume**)
Hiruma et al. (Cardiovascular Diabetology, 2021)	Empagliflozin	***No significant changes*** in in pericardial, epicardial, and paracardial fat content
Gaborit et al. (Cardiovascular Diabetology, 2021)	Empagliflozin	***No significant reduction*** in **EAT volume** in high-risk patients with T2D and normal LVEF
Cinti et al. (Cardiovascular Diabetology, 2023)	Dapagliflozin	**- 19%** reduction in **EAT thickness**

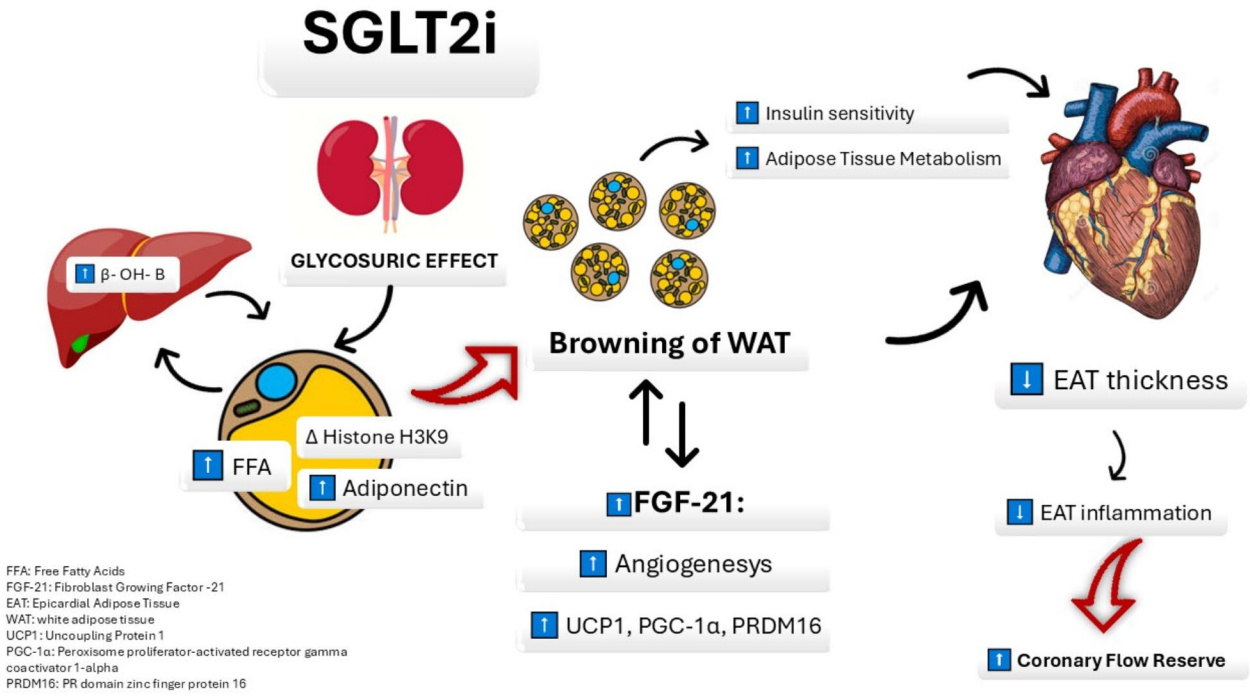


Fig. 1 SGLT2i, by inducing glycosuria, lead to the hepatic production of the ketone β-OH-B, which stimulates FFA production in adipose tissue. This process also modifies histone H3K9, leading to increased adiponectin levels and promoting the browning of white adipose tissue (WAT). Consequently, the activation of BAT increases the secretion of FGF21, promoting brown adipose tissue (BAT) activity and browning of WAT (confirmed by the increase of UCP1, PGC1α, and PRDM16 expression). When BAT activity increases, insulin sensitivity and metabolism are enhanced. All these effects are reflected in the cardiovascular system at epicardial adipose tissue (EAT) level, where SGLT2i induce a reduction in EAT thickness which leads to a reduction of EAT inflammation, improving coronary flow reserve (CFR)

adipose tissue metabolism. These findings underscore the role of SGLT2i in modulating adipocyte function, promoting the browning of white adipose tissue, and enhancing insulin sensitivity (Fig. 1).

SGLT2i exhibit a direct influence on adipose tissue, characterized by alterations in adipocyte cytokine production (adipokines), which enhance insulin sensitivity and mitigate the progression of T2DM. Furthermore, these medications have been linked to the redistribution of adipose tissue, favoring a reduction in visceral fat associated with metabolic benefits. This action suggests a decrease in the pro-inflammatory state of adipose tissue, offering a new pathway for mitigating the cardiovascular and renal risks associated with metabolic syndromes.

Therefore, the clinical relevance of SGLT2i encompasses cardiovascular protection, weight management, and renal benefits. Their role in improving heart function and reducing heart failure incidence highlights the potential of these drugs to play a decisive role in the multidisciplinary treatment of T2DM patients with high cardiovascular risk. Additionally, their renal protective effects make them a cornerstone of the current therapeutic arsenal.

Given the diverse benefits of SGLT2i, there are ongoing investigations in several areas. The mechanisms underlying the different effects on various adipose tissues, including epicardial adipose tissue, and their long-term implications for cardiovascular and metabolic health are areas still ripe for exploration. Considering all the direct or indirect beneficial effects on adipose tissue metabolism, further investigations should be conducted into the use of SGLT2i in all dysfunctional adipose tissue– related diseases, such as obesity, metabolic-dysfunction associated fatty liver disease (MAFLD), insulin resistance per se and even cancer, in which they could exert bidirectional benefits, namely removing the primary energy source of tumor cells (glucose) and improving adipose tissue metabolism whose dysfunction has been strongly associated with the development of several types of cancer [125].

Future research should thus focus on further investigation of the effects of SGLT2i on the adipose organ, beyond the conventional markers of T2DM control.

Abbreviations

CAD	Coronary artery disease
EAT	Epicardial adipose tissue
HF	Heart failure
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
T2DM	Type 2 diabetes
CV	Cardiovascular
MACE	Major adverse cardiovascular events

SAT	Subcutaneous adipose tissue
CFR	Coronary flow reserve
WAT	White adipose tissue
BAT	Brown adipose tissue
UCP 1	Uncoupling protein 1
FGF-21	Fibroblast growth factor 21
PCOS	Polycystic ovary syndrome
SOD2	Enzyme superoxide dismutase
PRDM16	PR domain-containing 16
FFAs	Free fatty acids
IL-6	Interleukin-6
TNF-r1	Tumor necrosis factor receptor-1
TNF-α	Tumor necrosis factor-α
PAI-1	Plasminogen activator inhibitor-1

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C.M, A.G and F.C wrote the main manuscript. S.G, U.C, G.D.G., T.M., G.C., S.M., L.S., M.B., A.A., A.S. and A.P. wrote parts of manuscript. C.M. prepared the graphical abstract. C.M., A.G. and F.C. edited and formatted the manuscript. All authors reviewed the manuscript.All authors have read and agreed to the published version of the manuscript.

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