SGLT2-Inhibitors on Epicardial Adipose Tissue

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Sodium–glucose cotransporter-2 inhibitors (SGLT2-i) reduce adipose tissue and cardiovascular events in patients with type 2 diabetes (T2D). Accumulation of epicardial adipose tissue (EAT) is associated with increased cardio-metabolic risks and obstructive coronary disease events in patients with T2D. Studies suggest that the amount of EAT is significantly reduced in T2D patients with SGLT2-i treatment.

Keywords: epicardial adipose tissue ; sodium–glucose co-transporter-2 inhibitors

1. Introduction

A close link exists between type 2 diabetes (T2D) and cardiovascular disease. Cardiovascular disease is the most prevalent cause of morbidity and mortality among people with type 2 diabetes [1].

There is growing evidence concerning the importance of epicardial adiposity in cardiometabolic risk. Epicardial adipose tissue (EAT) is composed of the adipose tissue depot immediately adjacent to the myocardium. Studies suggest that excessive EAT plays an important role in the genesis of coronary heart disease through potential paracrine or endocrine mechanisms by exerting inflammatory mediators, such as TNF-alpha, IL-6, adipocytokines, and leptin, which predispose to atherosclerosis [2][3].

Studies have shown that EAT is closely related to the extent and severity of coronary artery disease [4]. It is also associated with high-risk atherosclerotic plaque composition [5].

It is established that sodium–glucose cotransporter-2 inhibitors (SGLT2-i) provide effective glycemic control and have been shown to reduce atherosclerotic events, hospitalizations for heart failure, cardiovascular mortality, and the progression of chronic kidney disease. Large randomized controlled trials of SGLT2-i, empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS PROGRAM), and dapagliflozin (DECLARE-TIMI 58) have proven their efficacy in cardiovascular outcome in patients with T2D and high cardiovascular risk or established cardiovascular disease [6][7][8]. The effects of SGLT2-i expand far beyond these indications, and its use has been studied in the treatment of heart failure and chronic kidney disease, even in patients without diabetes [9]. The protective effects of SGLT2-i on the kidney are believed to be mediated by a number of both hemodynamic and nonhemodynamic mechanisms: reduction in blood pressure and vascular stiffness [10], restoration of the tubuloglomerular feedback [11], reduction in workload regarding ATP production [12], anti-inflammatory and antifibrotic effects, and reduction in oxidative stress [13].

In addition, these drugs are associated with body weight loss and can reduce abdominal visceral adipose tissue (VAT) [14].

Interestingly, the heart does not express SGLT2, but it is expressed in EAT [15]. Similarly, SGLT2-i increases glucose uptake, reduces the secretion of proinflammatory chemokines, and improves the differentiation of epicardial adipose tissue cells [15]. These data suggest a new potentially protective pathway for this group of drugs in cardiovascular disease. In other words, targeted pharmaceutical interventions with these antidiabetic drugs could help to return EAT to its physiological role.

2. SGLT2-Inhibitors on Epicardial Adipose Tissue

Abnormally accumulated visceral fat favors insulin resistance. This can lead to a reduction in insulin sensitivity, increase the secretion of proinflammatory cytokines in adipose tissue, and promote the development of cardiovascular diseases [16][17]. EAT is one of the visceral fat stores in the body, and some authors have suggested that measurement of EAT is a substitute for that of VAT [18]. A previously published meta-analysis suggests that the amount of EAT is significantly higher in T2D patients than in non-T2D patients [19]. Therefore, interventions designed for metabolic control in the patient with T2D could have a beneficial impact on EAT [20].

However, the results published to date are conflicting. Zsóri et al. reported that in new-onset T2D, metformin reduced fat deposits in the liver without an effect on the pericardium [21]. In addition, another report showed that pioglitazone, but not metformin, increased pericardial fat volume in T2D patients [22]. Conversely, some studies showed that liraglutide (an analog of glucagon-like peptide-1) and sitagliptin (a dipeptidyl peptidase-4 inhibitor), caused a substantial and rapid EAT reduction [23][24]. With the meta-analysis technique, our study analyzed all of the available evidence for the first time, exploring the effect of SGLT2 inhibitors on EAT.

In Gaborit et al. 2021, empagliflozin treatment did not reduce EAT, despite the reduction in BMI, Hba1c, and VAT. One possible mechanism when we compared Sato T et al. 2020 [25] and Sato T et al. 2018 [26] was the difference in body compositions between Asians and Europeans. Sato T et al. used CT imaging, and the follow-up occurred after 24 weeks, while Gaborit et al. 2021 used novel multiple cardiac imaging modalities combining 1H-MRS and 31P-MRS, and the follow-up occurred after 12 weeks [27].

In other research focusing on SGT2-i, we found three clinical trials in paired studies without control groups: Yagi S et al. [28], in which canagliflozin treatment reduced EAT by 20.34% in 24 weeks; Bouchi R et al. [29], in which luseogliflozin reduced EAT by 5.13% in 12 weeks; and Fukuda T et al. [30], in which ipragliflozin reduced EAT by 12.75% in 12 weeks. After these last studies, the BMI and HbA1c were reduced, but VAT levels were reduced in only two of the three studies. The reduction in EAT was higher than we expected. The precise mechanisms underlying these results are unknown. However, EAT has a higher rate of fatty acid intake and secretin than VAT and functions as a local energy source during times of energy demand. The high metabolic turnover might explain why EAT was more sensitive to SGLT2-i compared to VAT [31].

For decades, clinical decisions about the treatment of T2D have been based on glycemic control. This has changed due to trials demonstrating atherosclerotic cardiovascular disease and chronic kidney disease benefits independent of the glucose-lowering potential of medications [32]. The SGLT2 inhibitor has been recognized as one of the front-line treatment drugs by the new guidelines for the management of T2D [33][34]. As regard to mechanism(s) that might regulate a significant reduction in major cardiovascular events, SGLT2-i may mediate partly through metabolic effects and output volume changes. SGLT2-i prevents the kidneys' reuptake of glucose and sodium from the proximal convoluted tubule. These drugs lead to an average decrease in HbA1c of 0.6–1.2%, a weight loss of 1.5–2.5 kg, and reductions in SBP of 2.5–4.5 mm Hg [35][36]. Similarly, we found a reduction in triglyceride levels and an incremental increase in HDL levels. These results have also been found in a recent meta-analysis of 48 RCT with SGLT-i [37].

We found no differences in weight, partly due to the fact that in the studies of Sato T et al., the overweight population was studied, whereas in the Gaborit B et al. 2021 study, the population with grade I obesity was included. This could explain the lack of significant difference between the groups. It is important to note that EAT possesses characteristics in relation to the expansion of fat and BMI. The expansion of EAT is different from that of visceral and subcutaneous adipose tissue. Fat depot expansion for visceral and subcutaneous adipose tissue is dependent on adipocyte hypertrophy; however, EAT is dependent on hyperplasia [38]. Therefore, it is assumed that epicardial fat depots respond differently to lifestyle. This is supported by findings that exercise specifically reduces visceral fat depots and EAT volume, even in the absence of weight loss [39]. Moreover, SGLT2-i has been shown to reduce ectopic fat accumulation without changing body weight [40].

EAT has protective properties as a buffer in the coronary arteries and myocardium against lipotoxicity and glucotoxicity in normal conditions. Therefore, the main mechanisms by which SGLT2-i reduce the volume and function of EAT would be glycemic improvement, reduction in lipid values, and weight loss [41]. In addition, the effect of these drugs on inflammatory profile, with a lower production of inflammatory cytokines and a higher production of anti-inflammatory adipokines, may also be a factor in cardiovascular benefit [42][43].

3. Conclusions

The use of SGLT2-i results in a significant reduction in EAT volume in a population with T2D. The true role of EAT in the cardiovascular benefit observed due to the new antidiabetic drugs requires clarification in future studies.

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