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Research Progress on the Impact of SGLT-2 on Epicardial Fat

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Abstract. Epicardial adipose tissue (EAT) refers to a special type of coronary fat that is in direct contact with the myocardium and coronary arteries with no other tissue separating it.The results of many recent studies have shown that abnormal changes in the adipose tissue of the outer mucosa of the Heart play an important role in the development of various cardiovascular diseases, such as atrial fibrillation, coronary atherosclerosis, and electrical remodeling of the heart, as well as being closely associated with an increased risk of complications after surgery. However, SGLT - 2 inhibitors, a novel class of therapeutic agents, have demonstrated remarkable efficacy in ameliorating the pathological state of epicardial adipose tissue. This finding furnishes a novel mechanistic basis for the prophylaxis of cardiovascular diseases. This article will examine in detail the potential mechanism of action of the SGLT-2 inhibitor in improving the condition in the adipose tissue of the outer mucosa of the heart aiming to achieve the preventive effect against cardiovascular diseases.It seeks to provide new perspectives and evidence for the prevention and fight against cardiovascular diseases.

Keywords: Epicardial adipose tissue (EAT), SGLT-2, cardiovascular diseases

1. Introduction

Despite continued advances in medical technology, cardiovascular disease is still one of the leading causes of mortality and disability worldwide. Epicardial adipose tissue (EAT) is a special adipose tissue located on the surface of the heart and within the pericardium and plays an important role in the physiology and pathology of the heart. In addition to protecting the heart, it also performs endocrine functions. It is capable of secreting a spectrum of bioactive substances—including leptin, adiponectin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)—that are involved in the modulation of systemic and local endothelial function, coagulation, and inflammatory processes. In addition, adipose tissue is closely related to the structure and function of the heart. Diseases such as postoperative atrial fibrillation (PFC), heart failure, and Valve calcification are affected by the crucial role of this tissue in emergence and development, which in turn leads to a poor prognosis in patients, long-term hospitalization, and increased medical costs [1,2]. Adipose tissue plays an important role in the onset, development and final prognosis of cardiovascular disease (CVD). Adipose tissue is central in terms of fat infiltration and mitochondrial dysfunction. Patients with diabetes mellitus and metabolic syndrome tend to have thickening of the adipose tissue of the

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pericardium and functional disorders, as well as a higher incidence of cardiovascular diseases. The inhibitor SGLT-2 (SGLT-2i), as a new type of hypoglycemic drug that has been much discussed in recent years, not only reduces blood sugar levels, but also has a great protective effect on the heart. In particular, its impact on the cardiovascular system is recognized as a pivotal mechanism underlying myocardial protection and holds substantial significance for the management of cardiovascular risk.

2. The relationship between the volume of epicardial adipose tissue and the disease

Patients with diabetes mellitus often show an increase in the volume of fatty tissue in the outer shell of the heart. This condition is closely related to body mass index (BMI). Appropriate studies have shown that the thickness of adipose tissue in the extracardial membrane correlates with the degree of myocardial fat infiltration. When infiltration becomes more pronounced, the likelihood of electrophysiological disorders and heart dysfunction in the myocardium increases, which leads to the gradual formation and development of atrial fibrillation [3]. Behind the appearance and development of coronary atherosclerosis there is also a significant participation in the increase in the volume of adipose tissue in the outer ovary. Atherosclerosis is the main pathological cause of cardiovascular diseases. Inflammatory mediators and oxidative stress byproducts released from this tissue directly impact coronary arterial endothelial cells, thereby triggering lipid accumulation and facilitating plaque formation and progression. It is an important "hidden helper". During the development of hypertrophy and heart failure, an increase in the volume of adipose tissue of the outer cardiac ovary plays a role that should not be underestimated. In conditions of hypertrophy, the myocardium under mechanical pressure directly harms cardiac activity, which manifests itself as high-risk factors for angina, fainting, and even sudden death; at the same time, the signal response of apoptosis generated in this case becomes more obvious over time. In the critical process of cardiac remodeling, the secretory products of the epicardium can directly modulate the physiological and metabolic mechanisms of the heart. Thanks to the action of the cell factor Transtra, it induces the process of fibrosis, thus exacerbating pathological changes and accelerating the increase in heart rate. The role of ESBU in the clinical management of patient diseases is of substantial significance.

3. The impact of SGLT-2 inhibitors on epicardial adipose tissue 3.1volume

In recent years, as research in the pathogenesis of cardiovascular diseases deepens, the important role of epicardial adipose tissue (EAT) is becoming increasingly apparent. This specific type of adipose tissue exhibits a close association with cardiac structure and function, while alterations in its volume are strongly linked to the onset and progression of various cardiovascular diseases. In this case, new sugar-reducing drugs, such as SGLT-2 inhibitors, have been shown to be effective in reducing the volume of adipose tissue in the outer shell of the heart, which has attracted much attention from researchers and clinicians [4].

3.1. Multi-pathway mechanism of action

SGLT-2 inhibitors have a significant effect on reducing the volume of epicardial adipose tissue in patients with diabetes [5]. This effect is due to the joint action of a multi-beam mechanism. After inhibition of sodium-glucose cotransporter 2, renal glucose reabsorption decreases, blood sugar levels decrease and large amounts of sugar are excreted in the urine. This mechanism of blood glucose utilization restricts the conversion of carbohydrates into adipose tissue and indirectly

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facilitates weight reduction, with a concomitant partial reduction in epicardial fat volume. At the same time, these drugs stimulate the secretion of glucagon. As a key hormonal regulator, glucagon modulates lipolytic enzymes in adipose metabolism, stimulates the hydrolysis of triglycerides in vivo into their constituent components—free fatty acids and glycerol—and ultimately facilitates their conversion into energy substrates for bodily utilization. This process concomitantly reduces fat accumulation, particularly in the epicardial region.

3.2. Comparative advantages over GLP-1 agonists

In addition, studies have shown that compared to other hypoglycemic drugs such as GLP-1 agonists, SGLT-2 inhibitors may have unique advantages in reducing the volume of adipose tissue in the outer shell of the heart. The GLP-1 agonist mainly acts on mechanisms such as delayed gastric emptying and appetite suppression to achieve weight reduction, which in turn indirectly affects the volume of adipose tissue in the heart [6]. However, in addition to reducing the fatty tissue of the outer mucosa of the heart by reducing blood sugar levels and weight, SGLT-2 inhibitors have unique hemodynamic effects. It can reduce renal blood flow and blood pressure, optimize the state of the whole body and microcirculation, reduce the load on the heart and thus have a positive effect on the fatty tissue of the outer membrane. This multifaceted mechanism makes SGLT-2 inhibitors more effective in regulating the volume of adipose tissue in the outer shell of the heart and lays the theoretical foundation for the prevention and treatment of cardiovascular diseases.

3.3. Significant effects in clinical trials

A series of clinical trial investigations have demonstrated that SGLT-2 inhibitors exert a significant impact on cardiovascular fat volume. For example, a randomized controlled trial showed that the reduction in pericardial fat volume in diabetics treated with SGLT-2 inhibitors was more significant than the control group treated with traditional sugar-lowering drugs. Advanced imaging techniques, such as magnetic resonance of the heart, help accurately record this change in volume. These results not only confirm the clinical value of such drugs, they are already creating a key basis for justifying the feasibility and effect necessary for future practical applications. Agnostics and experts in this field are relevant to this topic.

3.4. Potential benefits of long-term application

From the perspective of long-term clinical application, the sustained regulatory effect of SGLT-2 inhibitors on epicardial adipose tissue volume is anticipated to confer broader cardiovascular protective benefits to patients. With the extension of treatment time, the gradual reduction of epicardial adipose tissue volume may lower the risk of cardiovascular diseases such as atrial fibrillation, coronary heart disease, and heart failure in patients, improve their cardiovascular prognosis, and enhance their quality of life. Meanwhile, this also suggests that in clinical practice, for diabetic patients with increased epicardial adipose tissue, the rational application of SGLT-2 inhibitors may achieve better therapeutic effects, providing new strategies and options for the comprehensive management of these patients.

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4. The effects of SGLT-2 inhibitors on inflammatory responses in epicardial adipose tissue

4.1. Reduced expression of inflammatory factors

Epicardial adipose tissue (EAT) is not only a site for fat storage but also has active endocrine functions, capable of secreting various cytokines and inflammatory mediators such as leptin, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and adiponectin. These substances play crucial roles in regulating systemic and local endothelial function, coagulation, and inflammatory states. Studies have shown that compared to subcutaneous adipose tissue, the levels of adipogenic factors in EAT are significantly higher, making EAT more active in inflammatory responses [7]. For instance, Rick B. Vega et al. found that in diabetic patients treated with SGLT-2 inhibitors, the expression level of IL-6 in EAT was lower [8]. In vitro experiments on epicardial adipocytes also demonstrated that patients treated with empagliflozin showed a lower inflammatory response. This indicates that SGLT-2 inhibitors can effectively suppress the inflammatory response in EAT and reduce the production of inflammatory mediators.

4.2. Decreased number of inflammation-related gene transcripts

Other research investigations have also indicated that SGLT-2 inhibitors can downregulate the expression of acetyl-CoA carboxylase 1 (ACC1) by enhancing ketone body production, reduce the malonylation modification of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and further mitigate the inflammatory response in epicardial adipose tissue (EAT), thereby attenuating atrial fibrosis [9]. This provides a new mechanism for the anti-inflammatory and functional improvement of EAT by SGLT-2 inhibitors. Additionally, it has been observed that in patients treated with SGLT-2i, the number of transcripts of inflammation-related genes such as IL6, IL1R1, IL1RAP, CCL2, CXCL2, and TNFAIP3 in subcutaneous adipose tissue significantly decreased, and a similar trend of reduced gene expression was also observed in EAT, with the reduction of TNFAIP3 reaching statistical significance. This suggests that SGLT-2 inhibitors not only regulate the inflammatory state of EAT but may also have an impact on systemic inflammatory responses.

4.3. Regulation of immune cell infiltration

Further research conducted immunohistochemical staining for F4/80 macrophage markers on adipose tissue biopsy samples, revealing that the number of these macrophages in EAT was reduced in patients treated with SGLT-2i compared to those not treated. Additionally, the levels of Th1 and Th2 cells in EAT also decreased [10]. This indicates that SGLT-2 inhibitors can regulate immune cell infiltration in EAT, reduce the aggregation of inflammatory cells, and thereby further inhibit the occurrence and development of inflammatory responses. This finding provides deeper theoretical support for the application of SGLT-2 inhibitors in the prevention and treatment of cardiovascular diseases.

5. The impact of SGLT-2 inhibitors on the metabolism of epicardial adipose tissue

The metabolic status of the fatty tissue of the outer mucosa of the heart is very important for the health of the heart and its normal functioning.SGLT-2 inhibitors regulate metabolic pathways by optimizing the metabolic function of epicardial adipose tissue. SGLT-2 inhibitors can increase the level of lipid metabolism in the adipose tissue of the outer mucosa of the heart. This effect is achieved by suppressing the activity of SGLT-2 and downregulating the expression of sodium-

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glucose cotransporters, thereby impairing renal glucose reabsorptive capacity to reduce blood glucose levels. This method allows not only effective control of blood glucose in diabetics, but also a positive change in the metabolism of adipose tissue in the outer shell of the heart. In the context of epicardial adipose tissue, reducing the glycemic index modulates the activation status of enzymes involved in lipid catabolism. This, in turn, facilitates enhancement of the capacity for complete oxidation and breakdown of intracellular lipid molecules through cellular aerobic metabolic processes. At the same time, it can also reduce the degree of accumulation of fatty components in the area and increase the ability of their accumulation in all directions. At the same time, thanks to new inhibitors and other causes, mitochondria are stimulated to manage the entire development process. The specific-weight network method gradually improved and this tendency continued to expand and develop until a relatively stable and mature structure of the metabolic model was finally formed. The advantages of this method include a significant improvement of the overall structure and improvement of the heart.

6. Conclusion

Epicardial adipose tissue (EAT) exhibits unique anatomical localization and physiological properties. It actively participates in the initiation and progression of various cardiovascular diseases and can be quantitatively analyzed through imaging modalities. However, no clinical trials have yet demonstrated a significant association between SGLT-2 inhibitors and reduced incidence of cardiac diseases or related postoperative complications.

(1) In-depth Study of Molecular Mechanisms

Subsequent studies may deepen the understanding of the molecular mechanism of action of SGLT-2 inhibitors that act on the adipose tissue of the pericardium.It is worth exploring topics such as how this inhibitor regulates specific signaling pathways and gene expression, thus affecting the differentiation, proliferation and function of the adipose tissue of the pericardium. Leveraging techniques such as gene chips and proteomics, it is feasible to comprehensively analyze alterations in gene and protein expression within pericardial adipose tissue before and after treatment with this inhibitor, thereby identifying pivotal molecular targets and their regulatory factors. In addition, one cannot overlook the study of how this inhibitor interacts with its targets (such as the PI3K/AKT pathway and MAPK pathway), which may further reveal their role in controlling the level of metabolism and inflammation of adipose tissue in the pericardial cavity.

(2) Development of Personalized Treatment Strategies

As the understanding of the mechanism of action of SGLT-2 inhibitors deepens, personalized treatment strategies will improve in the future. Genetic testing and biomarker analysis are used to assess the pathophysiological state of the patient's pericardial adipose tissue and its potential response to sgld-2 inhibitors, and then to select people who are most likely to benefit from it. In cases where patients present with severe pericardial adipose tissue inflammation or marked metabolic disturbances, priority should be accorded to pharmacotherapy, with treatment regimens adjusted on the basis of follow-up data. In addition to that, adjusting individual doses and course duration based on other clinical characteristics of patients can help improve the safety and effectiveness of treatment.In this case, factors such as age and gender are also taken into account.

(3)Development of New SGLT-2 Inhibitors

Although existing inhibitors of SGLT-2 have shown more positive therapeutic effects, they are still limited to relatively short half-lives and kidney function requirements. Future studies may focus on this area, for example, on the development of compounds with a significantly longer Half-Life, which will reduce the frequency of drugs and thus improve patient compliance with drugs. At the

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same time, pay attention to the safety of drug use in the context of kidney disease, and develop a new type of inhibition of SGLT-2 to reduce damage to kidney function to ensure that such drugs can also have a safe effect on patients with poor kidney function. In addition, it is necessary to increase the selectivity of exposure to specific targets in order to limit non-specific toxic effects on other systems and maintain a more stable response to safety and drug tolerance. Furthermore, optimizing the properties and clinical efficacy of existing pharmaceutical agents is anticipated to further expand therapeutic options for cardiovascular diseases.

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