

SGLT2 Inhibitor And GLP-1 Receptor Agonist in Type 2 Diabetes Mellitus Patients. Research on Their Cardiovascular Benefits

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Abstract. The health of people is now seriously threatened by diabetes. Type 2 diabetes mellitus' patients are prone to microvascular diseases, which is a cardiovascular disease risk factor. In T2DM patients, it has been demonstrated that sodium-glucose co-transporters (SGLT2) inhibitors have positive cardiovascular effects, glucagon like peptide 1 (GLP-1) receptor agonist also exhibited similar effect on cardiovascular. In recent, noteworthy trials, GLP-1RAs and SGLT-2Is have demonstrated effective cardiac protection and safety in high-risk T2DM patients, which is a new force in T2DM drug therapy.

Keywords: Type 2 diabetes mellitus; SGLT2 inhibitors; glucagon like peptide 1 (GLP-1) receptor agonist; cardiovascular.

1. Introduction

As we all know, numerous clinical and physiological problems define type 2 diabetes mellitus. Its patients are prone to microvascular diseases, which is a cardiovascular disease risk factor. When compared to non-diabetics, the incidence of heart attack and stroke is increased two to three times. Diabetes heart disease is a common vascular complication of diabetes, mainly including diabetes coronary atherosclerotic heart disease, diabetes cardiomyopathy, diabetes cardiac autonomic neuropathy and so on. There is evidence that strict blood glucose control is not independently related to cardiovascular and renal complications and microvascular complications in diabetes. The management of other cardiovascular risk factors, such as hypertension and blood lipids, in diabetic patients, however, appears to be a more efficient method of preventing cardiovascular disease and mortality than rigorous glucose control. Therefore, more new hypoglycemic drugs focus on cardiovascular effects other than blood glucose. Among them, SGLT2i and GLP-1-RA have clear cardiac benefits. This article will introduce the benefits of SGLT2i and GLP-1-RA for cardiovascular disease in diabetes.

2. SGLT-2 inhibitor and GLP-1 receptor agonist

2.1. SGLT-2 inhibitor

SGLT2 inhibitors are antihyperglycemic medications that prevent heart disease and renal failure in people with type 2 diabetes and preserved or diminished kidney function [1]. Its main mechanism is through the glucose transporter located at the proximal end of the renal tubule [2], which participates in about 90% of the cycle of glucose reabsorption from the original urine back into the body. Some glucose remains after this process and is reabsorbed at the distal end of the renal tubule after transport via the SGLT1 transporter. It is not only beneficial to T2DM heart failure patients, but also has a protective effect on their kidneys.

2.1.1 Mechanism

Multiple sensitization mechanisms may be used by SGLT 2 inhibitors to exert their cardioprotective and renal [3] protective effects [4]: (1) It can inhibit the primary proximal tubular hyperabsorption of the kidney, glomerular hyperfiltration can be reduced, and albumin filtration and

renal tubular transport can be impacted, all of which can lower the amount of oxygen consumed by the kidneys; (2) SGLT2 inhibitors can lessen the development of proteinuria and renal inflammation by reducing blood sugar levels; (3) It has mild osmotic diuresis, natriuresis and uric acid-lowering effects, and is also related to vasodilation and improvement of endothelial function [5]. extracellular volume (ECV), blood pressure, serum uric acid levels [6, 7] and body weight, etc, illustrate its beneficial effects on the kidneys and cardiovascular system; (4) because of the functions of SGLT2 and sodium hydrogen exchanger 3 (NHE3) related, so SGLT2 inhibitors will also limit NHE3 in the proximal tubule, thereby altering the effects on natriuresis, blood pressure, health, and glomerular filtration rate (GFR); (5) SGLT2 inhibitors increase glucagon levels, reduce the dose of insulin used in therapy, and reduce the level of insulin requirements. As a result, there is an increase in hepatic gluconeogenesis and lipolysis. These metabolic changes could have a positive impact on the kidneys and the cardiovascular system by lowering adipose tissue/body weight and the risk of hypoglycemia.

2.1.2 Inhibit the onset of cardiovascular disease.

Anti-cardiac remodeling. The onset of heart failure is closely related to cardiac remodeling, in which cardiomyocyte fibrosis causes irreversible remodeling of the heart. According to studies, SGLT2 inhibitors reduce cardiac fibroblast differentiation while promoting macrophage activation, resulting in the blocking of the process of myocardial collagen fiber synthesis [8]. Oxidative stress and inflammation will increase the level of cell apoptosis, which may affect cardiac contractile function and cause surviving cardiomyocytes to undergo fibrosis in order to adapt to the cardiac state. SGLT2 inhibitors have anti-inflammatory and anti-oxidative stress effects. These drugs can reduce the expression of some inflammatory factors, reduce the occurrence of stress reactions, and thereby achieve the effect of anti-myocardial fibrosis. As a result, myocardial compliance and cardiac systolic and diastolic functions are improved.

Anti-adipokine. The pathogenesis of heart failure is related to the ectopic deposition of fat in the epicardium of the heart, and there is a close relationship between myocardial adipokines and this deposition process [9]. Studies have shown that the impact of myocardial inflammation varies depending on different adipokines. The adipokine leptin promotes myocardial inflammation, while adiponectin can inhibit the occurrence of myocardial inflammation [10]. SGLT2 inhibitors are important for the dynamic balance of anti-inflammatory and pro-inflammatory adipokines, which attenuate fat deposition in the cardiac epicardium by accelerating the restoration of balance. According to one study, adiponectin levels considerably rose in type 2 diabetics taking SGLT2 inhibitors, suggesting that SGLT2 inhibitors can protect the heart by increasing adiponectin expression [11]. By raising the expression of adiponectin and controlling the production of inflammatory markers, SGLT2 inhibitors can also stop the atherosclerotic process and improve the cardiovascular prognosis of patients [12].

SGLT2 inhibitors can improve cardiac load. SGLT2 inhibitors can improve the body's ventricular diastolic function by reducing fat deposition in the epicardium and reducing visceral fat content. In animal models, SGLT2 inhibitors can reduce left ventricular volume and thereby increase left ventricular end-diastolic diameter [13]. The majority of academics agree that the permeability of SGLT2 inhibitors plays a role in how they improve heart function. By promoting urination and sodium excretion, these substances significantly reduce interstitial fluid, thereby reducing cardiac load.

SGLT2 inhibitors can play a role in providing metabolic fuel. Under normal circumstances, the expression level of ketone bodies in plasma is low. They are mainly derived from the liver and are produced during the breakdown of fatty acids. When people are hungry, fatty acids are broken down and ketone bodies are produced to replace sugars as fuel. At the same time, compared to glucose, ketone bodies can produce more ATP when consuming the same amount of oxygen, improving the work efficiency of the heart. Ketone body synthesis is closely correlated with the use of SGLT2 inhibitors. According to studies, after taking dapagliflozin for three months, patients with T2DM had their levels of acetoacetate, free fatty acids, and -hydroxybutyrate checked. Dapagliflozin patients'

ketone body levels were discovered to be considerably greater than those of the control group [14]. Canagliflozin is being used by type 2 diabetics, according to another study, diabetes patients have much higher plasma concentrations of ketone bodies, and different canagliflozin dosages have variable effects [15].

2.1.3 SGLT2 inhibitor safety

Adverse reactions. When combined with other anti-diabetic medications, SGLT2 inhibitors may result in hypoglycemia. SGLT2 inhibitors can lessen a patient's reliance on insulin dosage in the therapy of T2DM. However, at the same time, insufficient insulin content in the body will cause more fat to be broken down into ketones. Excessive ketone levels may lead to ketoacidosis. Therefore, when using this type of drug, the ketone body content in the body should be monitored. Studies have also found that the use of SGLT2 inhibitors may also cause multiple complications, including acute pancreatitis, reproductive system and urinary tract infections [16]. If a patient develops the above complications while taking an SGLT2 inhibitor, the drug should be discontinued immediately and treated symptomatically.

Medication contraindications. The efficiency of SGLT2i in the therapy of T2DM is significantly influenced by the patient's renal function. Diabetic patients with severe renal dysfunction should not use this class of drugs. Since the functions of various organs in the elderly have deteriorated, the glomerular filtration rate should also be assessed before using SGLT2 inhibitors, and the dosage of such drugs should be reduced during administration to ensure drug safety while ensuring the blood sugar control effect [17].

3. GLP-1 receptor agonist

GLP-1 is a systemic hormone derived from the gut. It has a variety of glucose regulatory effects, can promote insulin synthesis and secretion, stimulate B cell proliferation and differentiation, and reduce B cell apoptosis [18], although it does not increase C-peptide levels, but it reduced the patient's insulin dosage, lowered postprandial blood sugar and body weight, and increased insulin sensitivity compared with the placebo group [19].

3.1. GLP-1 receptor agonist's impact on blood lipid levels and blood pressure

Patients with type 2 diabetes have an abnormal decrease in the activity of lipid metabolic enzymes, which can result in an abnormal increase in blood lipids. This abnormal decrease in activity is influenced by insulin resistance factors in the liver and fat cells. Furthermore, people with type 2 diabetes are more susceptible to obesity, consume more, exercise less, and have an increase in lipid production. As a result, there is a direct connection between hyperlipidemia and type 2 diabetes. [20]. And hyperlipidemia easily leads to plaque formation and deposition in the vascular wall, causing atherosclerotic heart disease, and even cerebral thrombosis. In addition, the occurrence of hypertension [21].

The pathogenesis is arteriosclerosis (thickening and hardening of the arterial wall, narrowing of the lumen, and reduction of elasticity, resulting in local blood supply shortage, and then hypertension), patients with T2DM experience signs of atherosclerosis in the majority of cases, as well as hypercoagulability, excessive fat, and other complications. Consequently, there is a direct connection between type 2 diabetes and hypertension [22]. As a result, in addition to hypoglycemia medication, lipid-lowering anti-hypertensive treatment is equally crucial for individuals with type 2 diabetes.

GLP-1 receptor agonists are incretins secreted by intestinal L cells. They can increase insulin secretion and reduce type 2 diabetes by decreasing intestinal lipid absorption and increasing hepatic fatty acid oxidation. Patients produce chylomicrons after meals, thereby reducing visceral fat accumulation [23]. Its significant lipid-lowering effect can reduce the negative impact of hyperlipidemia on cardiovascular disease and reduce cardiovascular damage and incidence. The study by Yu Yinan et al. [24] also confirmed that the association with islets of asparagus

Compared with GLP-30 injection, GLP-1-RA has more benefits for patients with type 2 diabetes in terms of lowering blood sugar, controlling blood lipids, and providing cardiovascular protection, and should be clinically promoted.

3.2. GLP-1 receptor agonists' effects on additional cardiovascular risk factors

Improve endothelial function: GLP-1-RA expression may have a protective effect on abnormal cells. Diabetic vascular disease exhibits lipodermal cell dysfunction (ECD) in its early stages due to inhibition of plasminogen activator inhibitor type 1 (PAI-1) and vascular adhesion of human vascular endothelial cells (HVEC) in vitro Molecule (VAM). Improve endothelial function by increasing the activity of nitric oxide synthase. [25].

GLP-1-RA is associated with coronary artery ischemia and ischemia-reperfusion injury. Firstly regulation of cell apoptosis: GLP-1-RA alleviates myocardial ischemia-reperfusion injury by inhibiting mitochondria-mediated endogenous apoptosis. In addition, vascular endothelial cells in contact with blood are a direct barrier and are more susceptible to ischemia-reperfusion injury after vascular recanalization. Liraglutide can inhibit the occurrence of Ca^{2+} overload in endothelial cells induced by hypoxia/reoxygenation, thereby reducing apoptosis. inhibit the occurrence of apoptosis and protect microcirculatory endothelial cells, ultimately reducing ischemia-reperfusion injury. Cellular hypoxia can induce apoptosis of microcirculatory endothelial cells by activating the inositol trisphosphate receptor (IP3R)- $[Ca^{2+}]_c$ /voltage-dependent anion channel (VDAC)- $[Ca^{2+}]_m$ damage signal, while GLP-1-RA can inhibit $[Ca^{2+}]_c$ / $[Ca^{2+}]_m$ overload and reduce cell apoptosis by regulating the endoplasmic reticulum IP3R protein [26]. On the other hand, regulate cell autophagy: Studies have shown that both exenatide and liraglutide can activate mammalian radon Parmycin target protein (mTOR)/Unc-51-like autophagy-activating kinase-dependent autophagy occurs, among which adenylate-activated protein kinase (AMPK)/mTOR are the two main factors of myocardial ischemia-reperfusion injury, thereby improving mitochondrial damage and cardiac function in diabetic rats, proving that GLP-1-RA can activate autophagy and thus exert a protective effect on cardiomyocytes. Finally regulate oxidative stress.

Atherosclerosis: by inhibiting the inflammatory response of macrophages, reducing the accumulation of monocytes/macrophages in the arterial wall may be related to reducing atherosclerotic lesions. Improving lipid distribution: Patients with type 2 diabetes dyslipidemia is a frequent issue, and it is a risk factor for cardiovascular disease. This may be because the intestinal mucosa's GLP-1 receptor has been activated, which reduces the release of apolipoproteins from chylomicrons and, as a result, lowers blood lipid levels [27].

3.3. Adverse reactions

Firstly, hypoglycemia and gastrointestinal adverse reactions: The main manifestations are nausea and vomiting, with the highest incidence rate of nausea, especially when first taking the drug. However, in most patients, the gastrointestinal symptoms will reduce or even disappear as time goes by. Discontinuation of medication due to gastrointestinal reactions is rare. Secondly, pancreatitis. Finally, medullary thyroid cancer: there is no proof that people receiving clinical treatment have a higher chance of developing multiple endocrine neoplasia type 2 syndrome or medullary thyroid cancer. Patients with severe symptoms should not take such medications [28].

4. Conclusion

In summary, SGLT2i and GLP-1-RA have demonstrated effective blood sugar-lowering and cardioprotective benefits in high-risk T2DM patients. Research data shows that less than 1/4 of global adult T2DM patients with cardiovascular disease have used hypoglycemic drugs that have been proven to have cardiovascular benefits, the status of treatment is worrying. While both SGLT-2 inhibitors and GLP-1-RA as novel antidiabetic agents have a cardiovascular benefit in patients with

T2DM. It seems that the combination of these two drugs will have greater benefits for T2DM patients, but clinical evidence is still insufficient, and we need more evidence to prove this.

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