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New advances in the application of sodium-glucose cotransporter-2 inhibitors in multisystem diseases

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Abstract: In recent years, the newly marketed sodium-glucose co-transporter 2 inhibitor (SGLT-2i) has received extensive attention, and has gradually been widely used in clinical practice because of its significant hypoglycemic effect. In addition to hypoglycemic effects, its obvious cardiovascular benefits and renal protection mechanisms, as well as its effects on weight loss, lowering blood uric acid, lowering blood pressure, and regulating blood lipids, have become the focus of clinical research. This article reviews the latest research and application progress of SGLT-2i in endocrine and metabolic diseases, circulatory system diseases, and tumor diseases.

1. Introduction

In recent years, with the deepening of clinical research on hypoglycemic drugs, SGLT-2i has begun to be favored by clinicians. As a new type of hypoglycemic drug, its hypoglycemic mechanism is not dependent on the secretion of insulin or increasing the sensitivity of insulin, but by inhibiting the reabsorption of glucose by the renal tubules in the human body, lowering the renal glucose threshold, thereby promoting excessive Glucose is excreted from the urine to maintain the body's blood glucose homeostasis [1]. Pharmacological studies on SGLT-2i have found that its main pharmacological effects include: lowering blood sugar and glycated hemoglobin (HbA1c), weight loss, lowering blood pressure, promoting uric acid and urinary sodium excretion, regulating blood lipids (elevating low-density lipoprotein cholesterol, high Density lipoprotein cholesterol, apolipoprotein A1 and apolipoprotein B), delaying the progression of kidney disease, etc., have different degrees of improvement in diabetes, cardiovascular disease and kidney disease [2], as shown in Table 1. This article reviews the latest progress in research and application of SGLT-2i in endocrine and metabolic diseases, circulatory system diseases, and tumor diseases, in order to deepen clinicians' understanding of the multiple effects of this drug, and for future clinical research on this drug. Provide ideas to maximize the clinical efficacy of the drug under the premise of rational application.

Table 1: Putative Extra-Glycemic Effects of SGLT2i

Action	Putative Mechanism
Blood pressure reduction	Osmotic diuresis and Natriuresis Reduction of arterial stiffness Improved endothelial function
Body weight reduction	Increased glucose excretion
Uric acid reduction	Reduced urate reabsorption
Ketone bodies increase	Glucagon secretion and suppression of insulin production due to lower plasma glucose level Direct effect on alfa cells
LDL and HDL cholesterol increase, triglycerides reduction	Increased lipoprotein lipase activity Accelerated clearance of VLDL Delayed turnover LDL
Liver steatosis amelioration	Reduction of liver fat content Reduction in hepatocyte injury biomarkers (AST, ALT, GGT)
Hematocrit increase	Reduction in plasma volume Increase in erythropoietin
Cytoplasmic sodium and calcium concentration decreased, mitochondrial calcium concentration increased	Na*/H*exchange inhibition
Cardiac fibrosis reduction	Reduction of oxidative stress M2 macrophage polarization Reduction of TGF-β
Epicardial adipose tissue volume reduction	Weight loss?Unknown mechanism
Oxidative stress reduction	Decrease in NADPH oxidase activity Lowering AGEs generation Improving mitochondrial function Improvement of glycemic control
Lowering proinflamatory cytokine expression	Improvement of glycemic control Weight loss Decrease in reactive oxygen species production
Arterial stiffness reduction	Weight loss Improvement of glycemic control Oxidative stress reduction Direct effects on vascular smooth muscle relaxation?
Endothelial dysfunction amelioration	Oxidative stress reduction Glucotoxicity reduction Direct effect on endothelium?

2. Application of SGLT-2i in endocrine and metabolic diseases

2.1. SGLT-2i and type 2 diabetes

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia and progressive dysregulation of the insulin-glucose feedback mechanism [3]. Sodium-glucose co-transporter-2 inhibitor (SGLT-2i) is a novel oral hypoglycemic drug for the treatment of hyperglycemia in T2DM. It reduces the reabsorption of urine glucose by inhibiting the expression of

SGLT-2 in proximal renal tubules, thereby reducing blood sugar [4]. In 2016, the "Chinese Expert Advice on the Rational Clinical Application of SGLT-2 Inhibitors" pointed out that: SGLT-2 inhibitors can be used in adult patients with type 2 diabetes. When metformin cannot be tolerated within a month, it can be used alone or in combination with other oral hypoglycemic agents and insulin [5].

2.2. SGLT-2i and diabetic nephropathy

Diabetic nephropathy (diabetic nephropathy) is one of the main microvascular complications of diabetes and one of the important causes of chronic renal failure[6-7]. The pathogenesis of diabetic nephropathy is still unclear. It is currently recognized that inflammatory mediators, innate immunity and autophagy play important roles in the occurrence and progression of diabetic nephropathy. A domestic animal test study confirmed that the SGLT2 inhibitor dapagliflozin can regulate innate immunity and exert anti-inflammatory, anti-apoptotic and autophagy-promoting effects by inhibiting the TLRs/MyD88 pathway, thereby alleviating renal injury in DN model rats [8]. With the continuous deepening of modern pharmacological research, SGLT-2i has been widely used in clinical practice. A domestic study [9] included 84 DKD patients who received dapagliflozin treatment and were followed up for more than 12 months. To optimize the effect of hypoglycemic therapy, some patients who use insulin can reduce the amount of insulin ($P<0.01$), and the results of this study suggest that dapagliflozin is relatively safe during the 12-month follow-up period, and can improve the blood sugar of patients, weight, blood pressure, and tend to reduce proteinuria, which is a good choice for DKD treatment. A clinical study on empagliflozin [10] included 84 DKD patients, who were divided into control group and observation group according to the principle of balance, with 42 cases in each group. The control group was selected for insulin therapy, and the observation group was additionally treated with empagliflozin on the basis of the control group. The results showed that empagliflozin could significantly reduce the level of urinary albumin in patients with DKD, improve renal function, and help delay the disease progression. Promote application value.

To sum up, SGLT-2i is widely used in diabetes and chronic kidney disease due to its unique hypoglycemic mechanism and its role in reducing inflammation, reducing proteinuria, and improving renal function in addition to hypoglycemic effects. Brilliant. However, some of the mechanisms of renal benefit have not been fully clarified, and due to insufficient clinical data and lack of evidence-based evidence, it has not become a commonly used drug in the treatment of chronic kidney disease. Therefore, we also look forward to continuous research and innovation in the future.

2.3. Weight loss and obesity of SGLT-2i

Since the advent of the first SGLT2 inhibitor, dapagliflozin, many researchers have also carried out various clinical experimental studies. While looking at its data from a series of trials on blood sugar control, the researchers also found its miraculous effect on weight loss. From some meta-analyses on the weight loss efficacy of SGLT2 inhibitors, it can be seen that the weight loss of diabetic patients ranges from 1.63 to 3.50 kg [11]. Taking canagliflozin as an example, a phase 3, randomized, double-blind, active drug controlled registration study included 1450 patients with type 2 diabetes mellitus under metformin background treatment in 157 centers in 19 countries. The canagliflozin 100 mg group, the canagliflozin 300 mg group, and the glimepiride 2 mg group were treated and followed up for 104 weeks. %, 4.2% and 0.9% [12]. It can be seen that the weight loss effect of SGLT-2i in diabetic patients is more obvious. In a phase 2 clinical trial involving 376 non-diabetic obese patients, patients taking placebo and canagliflozin 50, 100, and 300 mg lost 1.1, 1.9, 2.8, and 2.4 kg of body weight after 12 weeks, respectively [13]. It can be seen that SGLT-2i can also significantly reduce body weight in non-diabetic obese patients.

SGLT2 inhibitors increase the excretion of urine glucose to achieve direct hypoglycemia, and achieve weight loss through mechanisms such as osmotic diuresis, conversion of calorie loss and body metabolism, and reduction of insulin dosage[11]. Obesity, as a chronic metabolic disease, is mainly characterized by an increase in the volume of adipocytes in the body, an increase in the number of adipocytes, an abnormal increase in the percentage of body fat to body mass, and excessive local deposition [14-15]. The human body is ingesting more high-calorie foods, which leads to the accumulation of fat in the body, and obesity is born. Therefore, reducing the intake of high-calorie foods, increasing the body's calorie consumption, and accelerating the body's fat metabolism have become obesity treatments. The essential. Some scholars have devoted themselves to studying the calorie metabolism mechanism of SGLT-2i, and concluded that: SGLT-2i will cause more calorie loss while reducing blood sugar in subjects, which is far greater than that caused by other types of hypoglycemic drugs when reducing blood sugar. More heat is lost. The reduction of body heat will correspondingly lead to the reduction of body mass. In addition, studies have found that SGLT-2i can also cause weight loss by accelerating the body's fat metabolism. There is a study of Japanese patients with diabetes, and the participants are BMI. There is a study of Japanese patients with diabetes, and the participants are patients with type 2 diabetes with a BMI value of 30 kg/m2 on average, and they are all given dapagliflozin 5 mg/d orally. After 12 weeks, the body weight decreased by 1.3-2.3 kg. At the same time, the visceral fat meter was used to evaluate the distribution of abdominal fat. The final results showed that the area of visceral fat decreased significantly [16].

Therefore, the effect of SGLT2 inhibitor on promoting body calorie loss and enhancing body fat metabolism can theoretically be applied to the treatment of obesity caused by excessive calorie intake and massive accumulation of fat. However, I personally think that the current research on SGLT2 inhibitors still has problems such as lack of systematic clinical data support and insufficient evidence-based medical evidence for its weight loss effect. In addition, on the one hand, problems such as compensatory overeating in the current clinical research on weight loss of SGLT2 inhibitors need to be solved urgently; For patients with chronic diseases, the selection of SGLT2 inhibitors needs to be comprehensively considered and systematically weighed to give a rational drug regimen, which undoubtedly poses another problem for the application of SGLT2 inhibitors in obesity treatment. However, the miraculous effect of SGLT2 inhibitors in weight loss makes it have broad prospects in the field of obesity treatment, and scholars are expected to conduct in-depth research in the future.

2.4. SGLT2 inhibitors and hyperuricemia

Since the application of SGLT2 inhibitors, some scholars have focused on their effect on reducing blood uric acid. Meta-analysis showed that a variety of SGLT2 inhibitors including canagliflozin, empagliflozin, dapagliflozin, etc. can reduce serum uric acid levels by an average of 37.73 μmol/L, of which empagliflozin has the most significant reduction effect (45.83μmol/L) [17]. Relevant studies have found that almost all SGLT2 inhibitors can significantly reduce blood uric acid levels, of which 100 mg canagliflozin can reduce blood uric acid by 37.88 μmol/L compared with placebo, and 5 mg dapagliflozin can reduce blood uric acid compared with placebo. Serum uric acid was 37.81 μmol/L, and other SGLT2 inhibitors also had varying degrees of uric acid-lowering effect [18]. Hyperuricemia is caused by excessive levels of uric acid in the body. At present, the treatment of hyperuricemia is mainly based on reducing blood uric acid, while the effect of SGLT2 inhibitors in reducing blood uric acid is not as good as that of commonly used clinical drugs. The results of Davies et al. [19] showed that canagliflozin can reduce blood uric acid by 13% in all patients with type 2 diabetes compared with placebo, and reduce blood uric acid in 23.5% of patients to below 360 μmol/L. In patients with type 2 diabetes, canagliflozin can reduce the blood uric acid level by about 23.5%, and the blood uric acid level in 32.4% of the patients decreased to below 360 μmol/L. Studies have shown

that SGLT2 inhibitors can help reduce adverse cardiovascular events and delay the progression of type 2 diabetic nephropathy by reducing serum uric acid [20]. Therefore, SGLT2 inhibitors may be used in patients with type 2 diabetes and hyperuricemia. In addition, hyperuricemia is often associated with metabolic syndrome, which requires blood pressure control, lipid-lowering, and weight-loss treatments. The weight loss, enhancement of body fat metabolism, and antihypertensive effects of SGLT2 inhibitors can be used here.

The prospect of SGLT2 inhibitors in the treatment of hyperuricemia is unquestionable, but there is a lack of systematic clinical studies and insufficient evidence-based evidence. In the future, more clinical studies are needed to further explore the clinical benefits of reducing serum uric acid, in order to provide a more reliable basis for the application of SGLT2 inhibitors in hyperuricemia.

3. Application of SGLT2 inhibitors in circulatory system diseases

3.1. Cardiovascular benefits of SGLT2 inhibitors

Recently, many researchers have begun to pay attention to the cardiovascular benefits of SGLT2 inhibitors. The EMPA-REG OUTCOM study [21] found that empagliflozin can reduce all-cause mortality by 32%, cardiovascular mortality by 38%, and major adverse cardiovascular events (cardiovascular death, non-fatal death) in patients with type 2 diabetes complicated by cardiovascular disease. The incidence of myocardial infarction, stroke) was 14%, and the hospitalization rate for heart failure was 35%. Other related studies also confirmed that dapagliflozin also showed good cardiovascular benefits in patients with type 2 diabetes and cardiovascular disease. Although the cardiovascular benefit of SGLT2 inhibitors is supported by the results of many clinical trials, the mechanism of its cardiovascular benefit remains unclear. Some scholars believe that the possible mechanisms of its cardiovascular protection include: reducing blood volume, reducing blood pressure, reducing body weight, improving endothelial function, improving insulin resistance, delaying atherosclerosis, improving myocardial metabolism, anti-oxidative stress, and inhibiting inflammatory responses [22].

3.2. SGLT2 inhibitors and heart failure

Some scholars have studied the clinical benefits of SGLT2 inhibitors in patients with heart failure. A subgroup study of the heart failure population with diabetes and reduced ejection fraction [23] found that dapagliflozin can significantly reduce the risk of heart failure hospitalization by 36% and the risk of cardiovascular death by 45%. The DAPA-HF study [24] included heart failure patients with reduced ejection fraction (45% of whom were diabetic and 55% non-diabetic), and the results showed that dapagliflozin significantly reduced the risk of cardiovascular death by 18%, heart failure The risk of exacerbation is 30%, and this study confirms that the benefit for heart failure is the same regardless of whether the patient has diabetes [25]. The DAPA-HF study [26] is a multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial involving patients with cardiac function class II-IV who received standard 4744 patients with ≤40%, the primary endpoint of the study was worsening of heart failure and cardiovascular death. The follow-up was 18.2 months. The results of the study showed that compared with the placebo group, the dapagliflozin treatment group could significantly reduce the primary endpoint event. (HR=0.75, 95%CI: 0.65-0.85, P<0.001), patients in the dapagliflozin treatment group could also reduce the risk of all-cause mortality by 17% (HR=0.83, 95%C: 0.71-0.97, P= 0.022), in addition, the results also showed that treatment with dapagliflozin can improve the long-term prognosis of patients with heart failure regardless of whether they have type 2 diabetes. From this point of view, SGLT2 inhibitors are supported by clinical evidence in the treatment of heart failure. However, so far, it has not been recommended by guidelines

due to insufficient evidence-based evidence and unclear cardiovascular benefit mechanism.

3.3. SGLT2 inhibitors and hypertension

During the clinical application of SGLT2 inhibitors, their significant antihypertensive effects have received widespread attention. An RCT evaluating the effect of dapagliflozin on blood pressure in diabetic and hypertensive patients with poorly controlled blood pressure following renin-angiotensin-aldosterone system (RAAS) blockade, after 12 weeks in the dapagliflozin group (302 patients) Compared with the control group (311 cases), the SBP decreased by 3.1 mmHg, and the 24-hour average systolic blood pressure decreased by 2.9 mmHg [27]. A meta-analysis that included 6 RCTs (2098 patients with type 2 diabetes) to study the effect of SGLT2 inhibitors on 24-h ambulatory blood pressure found that SGLT2 inhibitors significantly reduced 24-h ambulatory systolic/diastolic blood pressure by 3.76/1.83 mmHg, systolic/diastolic blood pressure was also significantly reduced during the day and night, and different SGLT2 inhibitors had antihypertensive effects [28]. In fact, SGLT2 inhibitors have been approved by clinicians for use in patients with type 2 diabetes and hypertension. However, there are very few clinical studies on its pure use in hypertension, and the antihypertensive effect has not been confirmed by systematic clinical studies, so follow-up clinical trials are expected.

4. SGLT2 inhibitors and tumors

Studies have found that SGLT2 is expressed in certain types of tumors and may be involved in the uptake and utilization of glucose by cancer cells to promote the growth and proliferation of cancer cells [29-30]. In other words, SGLT2 inhibitors may inhibit the growth and proliferation of tumor cells. In theory, then, SGLT2 inhibitors may be used in cancer treatment.

In fact, after continuous animal experiments and clinical studies, SGLT2 inhibitors have recently been recognized as a potential anticancer drug. Scafoglio et al. [31] human pancreatic cancer cells and prostate cancer cells in mice and intervened with selective SGLT2 inhibitors. The glucose uptake of tumor cells was reduced, growth was blocked, and tumor cell necrosis occurred. Nakano et al. [32] conducted a multi-omics analysis of the effect of canagliflozin on the growth of liver cancer cells by metabolomics and absolute quantitative proteomics, and found that canagliflozin can alter the mitochondrial oxidative phosphorylation metabolism of liver cancer cells, Fatty acid metabolism, purine and pyrimidine metabolism, inhibits proliferation of hepatoma cells by regulating metabolic reprogramming. Okada [33] chose dapagliflozin to study colon cancer cells and found that dapagliflozin could induce cancer cells in colon cancer cells that expressed SGLT2 but not UGT1A9 (the biological enzyme that degrades dapagliflozin). The loss of adhesion ability resulted in shedding of cancer cells, which is consistent with their previous report that dapagliflozin treatment of cultured adherent cells induced cell detachment [34]. These studies have confirmed that SGLT2 inhibitors can exert anti-tumor effects such as inhibiting tumor cell proliferation in many cancers such as pancreatic cancer, prostate cancer, liver cancer, and colon cancer. In recent years, some researchers have focused on the effect of SGLT2 inhibitor combined with radiotherapy and chemotherapy in tumor treatment. Angelopoulou et al. [35] developed canagliflozin-loaded magnetic nanoparticles. In a mouse xenograft tumor model, canagliflozin-loaded canagliflozin was compared with unencapsulated canagliflozin combined with radiotherapy. Nanoparticles combined with radiotherapy (external magnetic field at the tumor site) showed higher antitumor activity. However, the specific mechanism still needs to be further studied in order to expand the tumor treatment methods and improve the clinical efficacy of radiotherapy and chemotherapy.

Recent clinical studies have shown that SGLT2 inhibitors have broad prospects in the field of tumor therapy. However, at present, because the mechanism of inhibiting tumor cell proliferation is still unclear, coupled with insufficient clinical evidence and inadequate design of some clinical trials,

there is still a long way to go for SGLT2 inhibitors to be used in tumor therapy.

Summary and prospect: As a new type of hypoglycemic drug, SGLT2 inhibitor has various effects on weight loss, blood pressure, blood uric acid, and blood lipid regulation in addition to hypoglycemic. It has broad application prospects in multi-system diseases such as hypertension, heart failure and tumors. Evidence-based medical studies have confirmed that it has good cardiovascular and renal benefits. So far, relevant guidelines have recommended SGLT2 inhibitors for type 2 diabetes, and recommended SGLT2 inhibitors in combination with type 2 diabetes and heart failure. or combined with chronic kidney disease. However, because the specific mechanism of action of the drug has not been fully confirmed, and the lack of systematic clinical studies and real-world research data has led to a lack of evidence-based basis, SGLT2 inhibitors have not been explicitly recommended for obesity, hyperuricemia and other above-mentioned diseases. However, with further research, the huge application potential of SGLT2 inhibitors in multisystem diseases will be fully realized.

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