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Effect of Sodium-Glucose Co-transporter 2 Inhibitor drugs on Cardiovascular Disease in Diabetes

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Abstract

Type 2 diabetes mellitus is a chronic metabolic illness linked to an increased risk of cardiovascular disease (CVD). Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a new class of anti-diabetic drugs that block glucose absorption from the kidney's proximal tubule, causing glycosuria.

Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are the four SGLT2I that are currently commercially accessible in various countries. SGLT2i has been proven to improve body weight, blood pressure, lipid profile, arterial stiffness, and endothelial function by reducing glycated haemoglobin by 0.5 percent to 1.0 percent.

SGLT2i has also been shown to have significant cardioprotective and renoprotective properties. The main mechanisms underlying their cardioprotective effects have been attributed to improvements in cardiac cell metabolism, ventricular loading conditions, inhibition of Na+/H+ exchange in myocardial cells, changes in adipokines and cytokines production, and a reduction in cardiac cell necrosis and fibrosis.

Urinary tract and vaginal infections, as well as euglycemic diabetic ketoacidosis, are the most common side effects of SGLT2i. Lower limb amputations, Fournier gangrene, the risk of bone fractures, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury have all been linked to SGLT2i.

Introductions

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which reduce renal glucose absorption in the proximal tubule of the nephron, are well-known treatments for type 2 diabetes mellitus (T2DM)[1]. Glucose excretion rises as a result, and blood glucose levels decline [2,3]. The cardioprotective effects of the SGLT2 inhibitors empagliflozin, dapagliflozin, and canagliflozin have been proven in large randomized studies in both diabetes mellitus and heart failure in the previous six years [4–9]. These findings appear to be supported by recent meta-analyses [10–12]. Empagliflozin was the first medicine to show a cardioprotective effect, reducing cardiovascular mortality and heart failure hospitalization (HF). Although there are several potential mechanisms for those favorable effects, the exact mechanism is unknown. [5–8,13]

Also exerted cardiovascular (CV) benefits. SGLT2 inhibitors also were shown to offer kidney protection in patients with diabetes and improve heart failure (HF) with or without diabetes [14,15].

Regarding the improved hemodynamic by SGLT2 inhibition, there are hypotheses postulating that these drugs lead to glucose and sodium reduction in the blood, resulting in an increase in urinary sodium excretion and reducing the reabsorption of both factors in the kidneys [16].

This impact reduces generalized congestion and intravascular volume while also lowering cardiac afterload and preload, leading to fewer HF hospitalizations. In most diabetes patients, the heart recognizes the utilization of free fatty acids as a substitute for glucose, but this compromises cardiac performance [17]. In this example, SGLT2 inhibitors have been shown to boost ketone production, with ketones being suggested to improve cardiac energetics and efficiency [18].

On-going research studies are conducted to shed more light on the relevance of the ketone hypothesis.

Sodium-glucose co-transporter 2 inhibitors

SGLT2 is a Na*-glucose cotransporter found almost entirely in the renal tubule's proximal part. SGLT2 is a high-affinity, low-capacity glucose transporter that uses energy generated by Na* flow through epithelial cells to transfer glucose across a concentration gradient from the tubular lumen. In non-diabetic people, renal glucose retention is practically complete, and SGLT2 accounts for 80 percent to 90 percent of it; the rest is retrieved by SGLT1 further down in the tubule.

Early studies in diabetic animals demonstrated that hyperglycaemia could be nearly ameliorated by the naturally occurring compound phlorizin, an SGLT inhibitor. Based on this proof of principle, drugs that are specific inhibitors of SGLT2 have been developed to treat diabetes.

These agents block glucose transport in the proximal tubule and lower blood glucose by promoting urinary loss.[19]

Mechanism of action of sodium-glucose co-transporter 2 inhibitors

SGLT2 is located almost exclusively in the kidney, while SGLT1 transporters are also found in the intestines, heart, and skeletal muscles(20). Glucose reabsorption in the kidneys occurs.

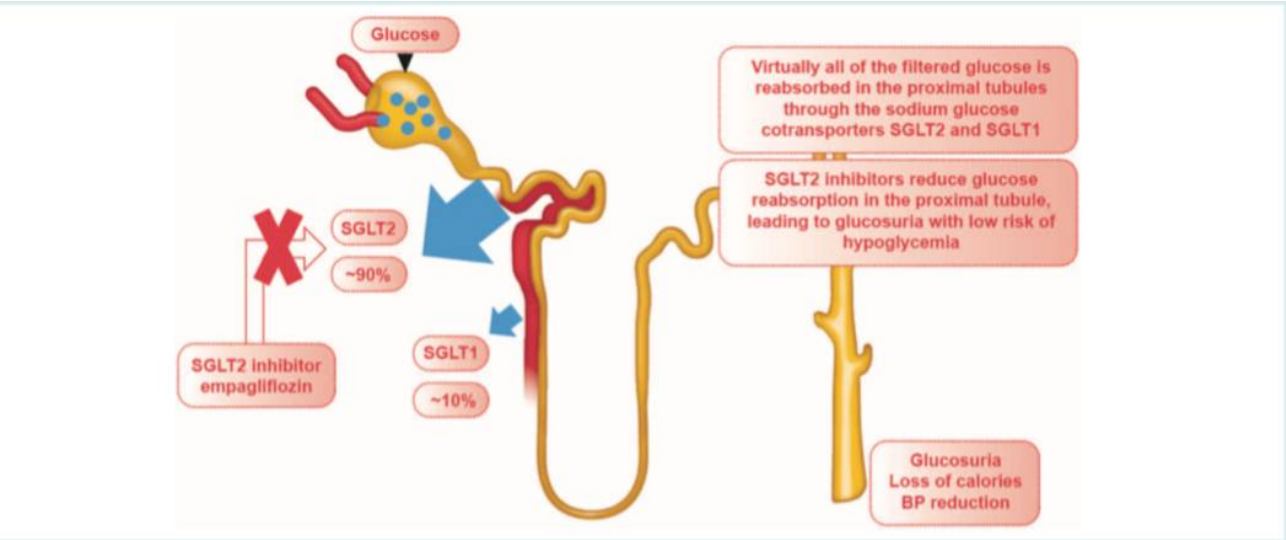

figure.1 mechanism of action SGLT-2 inhibtors

in a sodium-dependent manner via SGLT proteins, with most reabsorption occurring at the proximal convoluted tubule through SGLT2 and a smaller portion in the distal segment of the proximal tubule by SGLT1.(21)

Once the maximum glucose transport capacity has been reached, excess glucose is excreted into the urine. SGLT2 inhibitors, therefore, lead to increased urinary glucose excretion by blocking SGLT2-mediates glucose reabsorption. (figure.1)

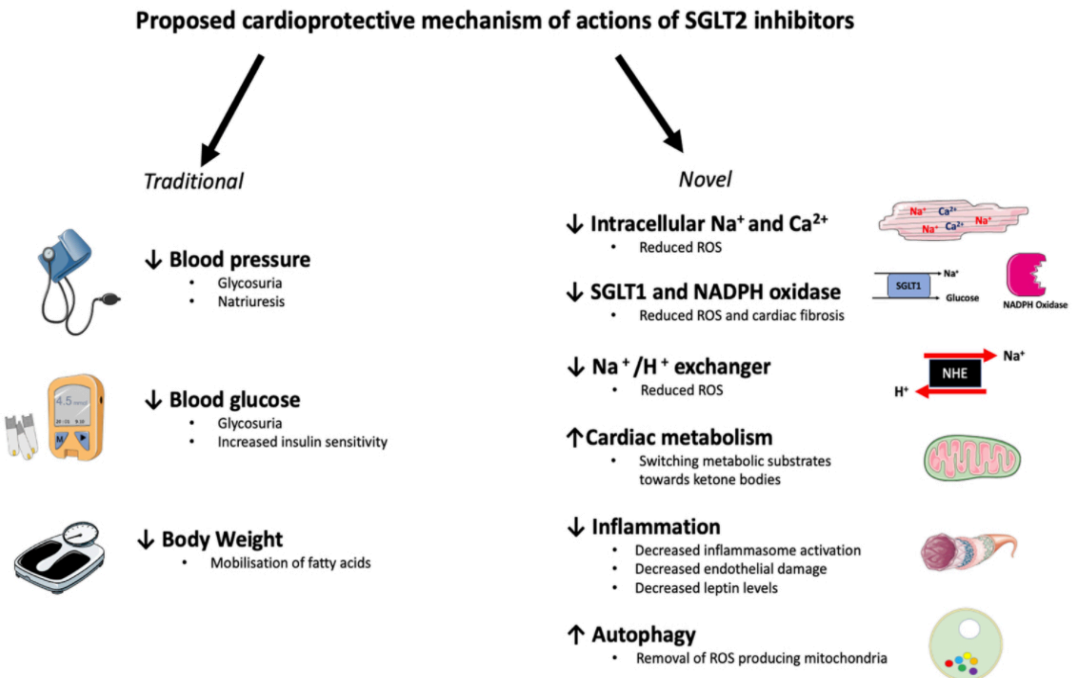

Figure.2 Mechanisms of Cardiovascular protective of SGLT2 inhibitors

Blood Pressure

Hypertension leads to increase in peripheral vascular resistance and afterload, and these changes in turn lead to left ventricle (LV) remodelling. Initially, LV hypertrophy ensures the cardiac output is maintained; however, decompensation of the remodelled LV ensues and can lead to HF over time. Therefore, it would logically follow that the reduction in blood pressure would yield more favourable heart failure outcomes.

Blood-pressure reduction by SGLT2 inhibitors is assumed to be related to their osmotic diuretic effect, although they have very slight natriuretic effects compared to diuretics. However, if osmotic diuresis were the sole mechanism, then the antihypertensive effect would diminish as kidney function deteriorates, but this is not the case. The decrease in systolic blood pressure at one month was accompanied by an increase in urinary volume and urinary excretion of both glucose and sodium, as well as body weight loss [22]

Over a longer course, a further reduction in body mass, owing to loss of visceral and subcutaneous adipose tissue, modulation of the RAAS, and reduced plasma uric acid levels is likely to reduce blood pressure [23].

The effects of administration of SGLT2 inhibitors after six months lead to lowering blood pressure is considered to be due to decrease the plasma volume resulting from both urinary sodium excretion and improvement of vascular endothelial function secondary to body weight loss [22]

Weight reduction and glycemic control

Chronic hyperglycemia can lead to the development of coronary heart disease, which can eventually lead to heart failure. Weight loss and exercise are still the most effective first-line treatments for T2DM. SGLT2 inhibitors were originally designed to help people manage their blood sugar levels. Following SGLT2 inhibitors, glycosuria causes volume loss and mobilizes fatty acids from adipose tissue.

SGLT2 inhibitor medication has been proven to lower body weight in people with T2DM in several clinical trials [24]. Therefore, the SGLT2 inhibitors induce weight loss, increase insulin sensitivity and lower blood glucose levels, that lead to improving heart failure outcomes.

The results of the DAPA-HF trial [25], which showed that there was a decrease risk of worsening heart failure or death from cardiovascular causes in both diabetic (HR 0.75, 95% CI 0.63–0.90) and non-diabetic (HR 0.7, 95% CI 0.60–0.88) patients, the hypothesis linking improved glycemic index to favourable heart failure outcomes has been reconsidered.

Cardiac Energy Metabolism

Hypoxia may cause a shift in glucose metabolism to anaerobic glycolysis, resulting in a decrease in the generation of adenosine triphosphate (ATP) [26]. Initially, heart illness is linked to adaptation in order to compensate for and reduce damaging processes. Chronic activation, on the other hand, will result in decompensation and the progression of heart failure [27].

Glycuria and hypoglycaemic effects are induced by SGLT2 inhibitors, which accelerate endogenous (hepatic) glucose production (EGP), fat oxidation, lipolysis, and ketogenesis while lowering total glucose dissociation (TGD) and glucose oxidase activity (GOx) [28]. As a result, glycosuria causes a change in whole-body metabolism to lipid mobilization and consumption, which is not unique to diabetes individuals [28].

Effects on Cardiac Ionic Homeostasis

Calcium ion (Ca2+) homeostasis in cardiomyocytes is maintained by inflow via the mitochondrial Ca2+ uniporter (MCU) and efflux via the mitochondrial Na+/Ca2+ exchanger (mNCE) [29]. Overloading the cytoplasm with sodium ions (Na+) causes this route to be disrupted. It lowers the redox potential of nicotinamide adenine dinucleotide phosphate [NAD(P)/NAD(P)+] and increases oxidative stress [30]

Despite the lack of SGLT2 expression in cardiomyocytes, empagliflozin has been shown to reduce cytoplasmic Na+ and Ca2+ burdens while increasing mitochondrial Ca2+ by inhibiting Na+/hydrogen ion (H+) exchange (NHE) directly [31]. SGLT2 inhibitors, such as dapagliflozin and empagliflozin, have been shown to boost the activity of the sarcoplasmic endoplasmic reticulum Ca2+-ATPase (SERCA2a), which is responsible for Ca2+ reuptake, resulting in improved left ventricular diastolic function [31].

Decreased inflammation

SGLT2 inhibitors have been shown to reduce biomarkers of inflammation in animal models.[32] In a rat model, the anti-inflammatory effects may be mediated by inhibiting NADPH oxidase activity and decreased formation of advanced glycation end products." This may benefit both the sequelae of T2DM and HF, such as vascular dysfunction and fibrosis.[33]

Renoprotective Effects of SGLT2 Inhibitors

SGLT2 inhibitors reduce glucose and Na+ reabsorption in the proximal convoluted tubule and increase natriuresis in the proximal tubule's late straight segment .As a result, these activities increase sodium concentration in the distal macula [34], which acts as a stimulant for tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction and decreased intraglomerular hypertension (Fig. 3). This mechanism could explain why SGLT2 inhibitors have been shown to have significant long-term kidney preservation.

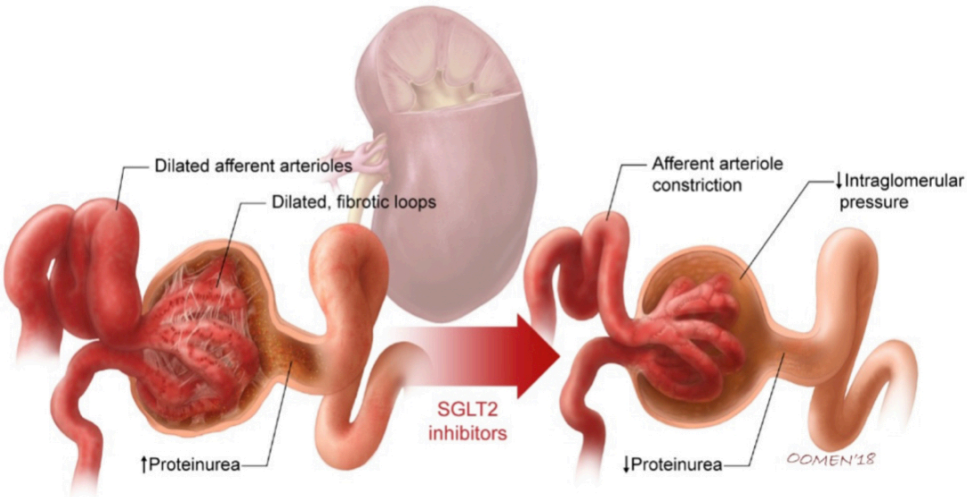

Figure.3 Renoprotective Effects of SGLT2 Inhibitors

Efferent arteriolar vasodilation is caused by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. When used with SGLT2 inhibitors, it is expected to have a co-incidence on intra glomerular pressure. It's possible that this explains why patients' eGFR drops at first, then plateaus over time. Diabetes is associated with an increase in whole-body sodium content, and the SGLT2 inhibitor dapagliflozin has been shown to lower tissue sodium content in persons with type 2 diabetes in recently completed translational studies in humans.

Effects on Cardiac Oxidative Stress

Overproduction of reactive oxygen species (ROS) due to mitochondrial malfunction, increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthase, and insufficient endogenous antioxidants is referred to as oxidative stress.

SGT2 inhibitors are implicated in decreasing the levels of some key oxidative stress biomarkers, prostaglandin-F2 and 8-hydroxy-2′-deoxyguanosine [35], leading to enhanced heart function and survival, according to a recent comprehensive review.

Autophagy

Autophagy and cardiovascular disorders have a complicated interaction. Although basal autophagy is important for cell homeostasis, both excessive elevations and decreases in autophagy can cause changes in normal heart and blood vessel activities [36]. Hypoxia, oxidative stress, infection, endoplasmic reticulum stress, and nutritional deprivation all trigger autophagy [37]. Autophagy dysregulation is linked to a variety of diseases, including cardiovascular disease. In animal investigations, SGLT2 inhibitors were found to decrease cardiomyocyte autosis (autophagic cell death) and have cardioprotective benefits. Treatment with empagliflozin reduced infarct size and myocardial fibrosis in myocardial infarction mice models, resulting in enhanced cardiac function and survival.

[**36**]. During ischemia and nutritional glucose deprivation, when autosis is set in high gear, empagliflozin directly inhibits the Na+/H+ exchanger 1 (NHE1) activity in the cardiomyocytes to regulate excessive autophagy. In primarily isolated cardiomyocytes, empagliflozin improved myocyte contractility without affecting their beating frequency [**38**]. Heart failure is associated with up regulation of NHE1 activity in the myocardium, with resultant increased cytosolic sodium and calcium concentrations in cardiomyocytes and increased oxidative stress and arrhythmogenesis, SGLT2 inhibitors may have therapeutic use

Additional hypotheses thought to be implicated in SGLT2 inhibitor-mediated cardioprotection

Reduced plasma uric acid

Increased uric acid is associated with poor prognosis in heart failure via several suggested pathways, including increased ROS, inflammation, and endothelial dysfunction. Glycosuria results in concomitant uric acid secretion, resulting in reduced plasma uric] acid levels, thus leading to favourable heart failure outcomes.[39]

Erythropoiesis

The observation that hematocrits is increased following SGLT2 inhibitor therapy led to the hypothesis that an increase in erythropoietin might result in more oxygen delivery to the myocyte and better mitochondrial function[40]

Decreased sympathetic stimulatio

The lack of a compensatory increase in heart rate after SGLT2 inhibitor therapy led to the conclusion that these drugs may reduce sympathetic activity.
Reduced norepinephrine turnover in brown adipose tissue and tyrosine hydroxylase (the rate-limiting enzyme in catecholamine production)[41] were suggested as possible causes of decreased sympathetic stimulation in preclinical studies.

Adverse Effects

The mechanism of action of SGLT2 inhibitors predicts their negative effects. Lower urinary tract infections have increased slightly (1 percent to 2%), while genital mycotic infections have increased by 3% to 5%. In a tiny percentage of patients, mainly the elderly, urine glucose losses induce moderate diuresis, which leads to hypotension and other symptoms. Because SGLT2 inhibitors are ultimately dependent on the rate of glucose

filtration to be effective, effectiveness drops by 40% to 80% across the stage 3 renal disease spectrum (GFR 60-30 mL/min). SGLT2 inhibitors do not cause hypoglycemia but can increase that likelihood when combined with drugs.

Clinical investigations with SGLT inhibitors have recently revealed that they may increase the incidence of fractures (FDA warning). These medications appear to impact mineral balance, circulation parathyroid hormone levels, and 1,25-hydroxyvitamin D levels, according to early studies. Studies are being conducted to determine whether this is a significant issue. Rare incidences of diabetic ketoacidosis have been recorded in patients taking SGLT2 inhibitors. There was no indication that SGLT2 inhibitors had any negative effects on cardiovascular disease in phase 3 clinical studies.
Data from controlled trials indicate that empagliflozin and canagliflozin reduce the risk for major cardiovascular events. Canagliflozin is associated with an increased risk of lower extremity amputation [19]

Conclusions

In summary, as a new category of drug for diabetes mellitus type 2 treatment, SGLT2 inhibitors are good hypoglycaemic agents that can lower the risk of cardiovascular disease and, in addition to, benefits cardiovascular and renal function. SGLT2 inhibitors can exert their cardiovascular protective effects by the super fuel theory, electrolyte factors and improved hemodynamics, elevate erythropoietin, increase glucagon, and decrease oxidative stress and inflammation. However, further research is required to clarify the particular mechanisms.

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