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Inhibitors of sodium-glucose transport protein 2: A new multidirectional therapeutic option for heart failure patients

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Abstract

Several mechanisms have been suggested to explain positive cardiovascular effects observed in studies with sodium-glucose co-transporter 2 (SGLT2) inhibitors. The reduction in glucose reabsorption in proximal tubuli induced by SGLT2 inhibitors increases urinary glucose and sodium excretion resulting in increased osmotic diuresis and consequently in decreased plasma volume, followed by reduced preload. In addition, the hemodynamic effects of SGLT2 inhibition were observed in both hyper and euglycemic patients. Due to the complex and multidirectional effects induced by SGLT2 inhibitors, this originally antidiabetic group of drugs has been successfully used to treat patients with heart failure as well as for subjects with chronic kidney disease. Moreover, their therapeutic potential seems to be even broader than the indications studied to date. (Cardiol J 2023; 30, 1: 143–149)

Key words: sodium-glucose co-transporters (SGLTs), dapagliflozin, empagliflozin, heart failure, mechanisms

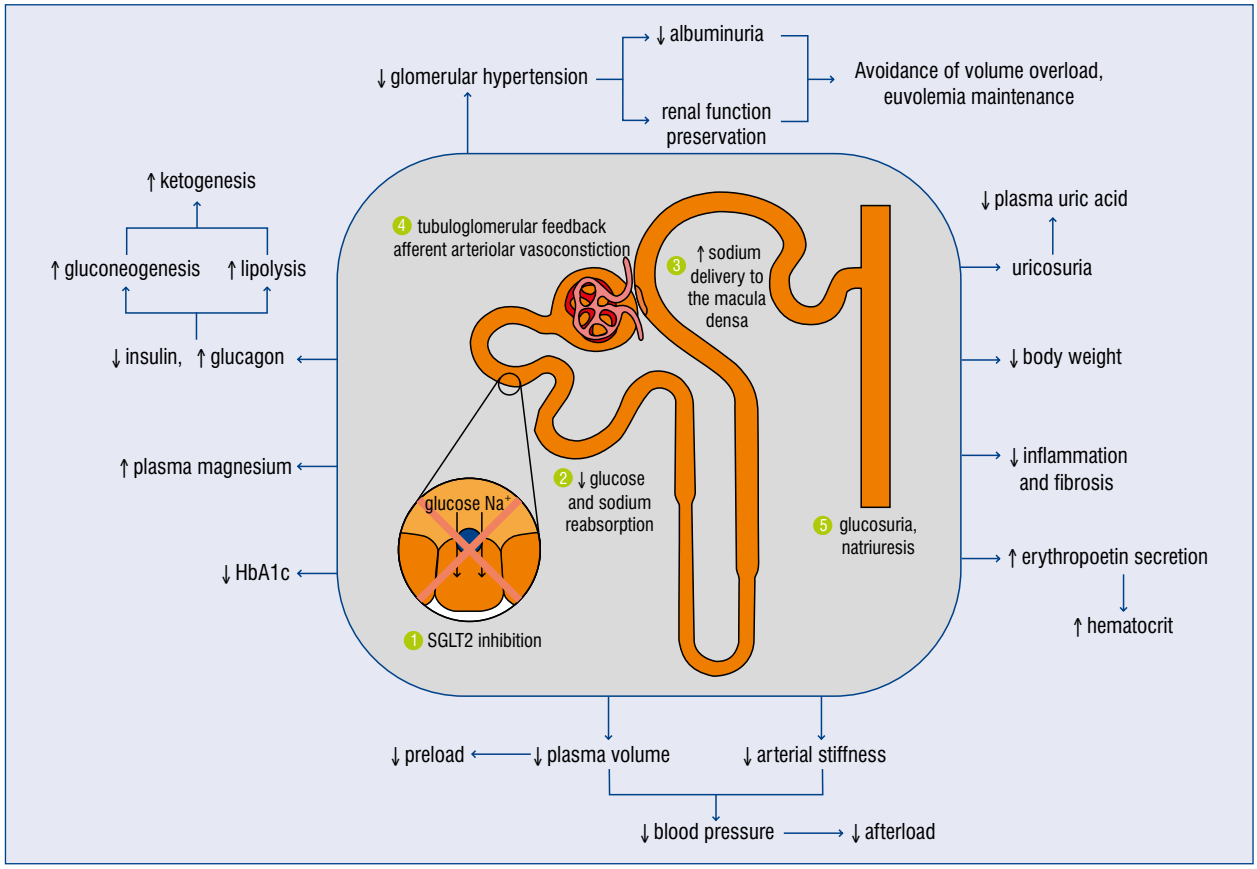
Sodium-glucose co-transporters

Sodium-glucose co-transporters (SGLTs) are a family of transmembrane proteins characterized by a shared transportation mechanism, in which extracellular sodium binding triggers a gate to open and trap glucose from outside the cell. Subsequently, the transporter flips releasing glucose and sodium into the cytoplasm. At the end of the process the protein returns to its initial conformation. SGLT1 and SGLT2 are the two most known SGLTs [1].

The SGLT2 is mainly expressed in the kidneys on the epithelial cells in the proximal convoluted tubule. In spite of low affinity for glucose, the SGLT2-mediated renal reabsorption demonstrates a very high capacity [2]. The reabsorption of glucose can be characterized as sodium-dependent with ratios of 1:1 and 2:1 for SGLT2 and SGLT1, respectively [1]. With only a fraction of tubular glucose reabsorption being SGLT1-mediated, the majority of the process, approximately 90%, is handled by SGLT2. The kidney capacity of reabsorbing of filtered glucose represents an extremely efficient mechanism of energy conservation. In addition to the kidney, the SGLT2 expression was demonstrated in the brain, liver, thyroid, muscles, and heart, while the SGLT1 expression was found in the intestine, trachea, kidney, heart, brain, testis, and prostate [1].

Sodium-glucose co-transporters inhibition

The first description of phlorizin's ability to block renal glucose reabsorption in humans was published in 1933 [3]. Phlorizin is a glucoside of phloretin (a bicyclic flavonoid), which can mainly be found in apples, specifically in unripe fruits and root bark, as well as in smaller quantities in strawberries. Phlorizin, a competitive nonspecific SGLT inhibitor, competes for binding with D-glucose. It reduces both postprandial and fasting glycemia as shown in experimental animal model studies [4]. Due to these properties, orally active selective inhibitors of SGLT2 have been applied as antidiabetic agents. The glucose reabsorption limited by SGLT2 inhibitors (SGLT2i) is characterized by the rapid onset of glycosuria (1–2 h), the dose-dependent offset of action in the range of 24–48 h and the glycemia-dependent entity of glycosuria. Inhibition of SGLT2 lowers the renal glucose threshold into the euglycemic range. In humans, glucose reabsorption inhibition can maximally reach between 30% and 50% [5]. Glycosuria induced by SGLT2i in diabetic patients results in further metabolic changes. The decrease in fasting and postprandial plasma glucose concentrations is caused by a partial drainage of glucose from the extracellular space. Plasma insulin concentration and the secretion rate declines while plasma glucagon rises following the glycemia changes. A decreased insulin-to-glucagon ratio alters hepatic glucose metabolism, inducing endogenous fasting gluconeogenesis and attenuating its postprandial suppression [1]. Lower insulin levels reduce the lipolysis inhibition and cause an excess of free fatty acids to reach the tissues via the bloodstream. The extra free fatty acids delivery, together with the insulin-to-glucagon ratio reduction translates into ketogenesis [5, 6]. Normally, the excess of free fatty acids would lead to insulin resistance by competing with glucose utilization. However, on treatment with SGLT2i it is paradoxically associated with improved insulin sensitivity [5, 7, 8]. A schematic presentation of SGLT2 inhibitors' mechanism of action is shown in the Central illustration.



Central illustration. Mechanisms of action of sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Clinical effects of sodium-glucose co-transporters inhibition

The loss of glucose on SGLT inhibitors channels into a substantial, between 250 kcal/day and 450 kcal/day, whole-body deficit of energy. However, based on this negative calorie balance, the weight loss observed in clinical trials was far less than expected, which might be explained by an increased caloric intake [9]. Countering this increase, through e.g., dietary counseling or pharmacological appetite quenching, could potentially strengthen the weight loss induced by SGLT2i [6, 9]. Complex metabolic changes induced by SGLT2i, including delayed clearance of low-density lipoprotein cholesterol (LDL-C) from the circulation along with increased plasma lipoprotein lipase activity, lead to increase of LDL-C and decrease of triglycerides plasma levels [8].

Additional properties of SGLT2i include a dose-dependent reduction of serum uric acid levels [10] as well as a reduction of urinary albumin excretion in type 2 diabetes patients with prevalent micro- or macroalbuminuria [11].

Several mechanisms have been suggested to explain positive cardiovascular effects observed in studies with SGLT2i [1, 6, 12–14]. Heart failure (HF) is a condition characterized by excessive accumulation of fluid in the vascular compartment as well as in the interstitial space. Still, many patients suffering from HF experience arterial underfilling due to a low cardiac output, which sometimes can be intensified by conventional treatment with diuretics. The reduction in glucose reabsorption in proximal tubuli induced by SGLT2i increases urinary glucose and sodium excretion resulting in increased osmotic diuresis and consequently in decreased plasma volume, followed by a reduced preload [6, 15].

Concomitant lowering of arterial stiffness and blood pressure leads to the afterload reduction [6, 15]. Sympathetic activation as well as decreased arterial filling, organ perfusion and blood pressure constitute some of the potential negative effects of excessively reducing blood volume [16]. However, heart rate has not been found to increase on treatment with SGLT2i despite the consistent fall in arterial blood pressure in patients with type 2 dia-

betes, indicating that autonomic balance shifts toward the parasympathetic branch [1]. According to experimental studies, a more significant reduction of interstitial fluid volume than that of blood volume can be observed with SGLT2i. Hence, they could serve as better congestion control agents without diminishing arterial filling and tissue perfusion in contrast to conventional diuretic treatment [16]. The beneficial effect of SGLT2i on left ventricular (LV) systolic (an increase of LV ejection fraction) and diastolic (a decrease of LV filling pressure) function was shown in patients with HF. Moreover, a significant decrease in LV mass index, left atrial volume index was observed. These findings were associated with a significant decrease in plasma B-type natriuretic peptide concentration only in patients with a baseline value ≥ 100 pg/mL [17].

The hemodynamic effects of SGLT2 inhibition were observed in both hyper and euglycemic patients [1, 5]. Regardless of these favorable changes a decrease of hemoglobin A1c (HbA1c) concentration, body weight, and blood pressure, as well as an increase in hematocrit, hemoglobin and albumin concentration, were noted [1, 5, 12, 18–20].

It has been proposed that the SGLT2 inhibition driven effects can be explained by the restoration of both the anabolic and catabolic states cycling and the housekeeping processes of the cells, which are facilitated by caloric offloading through glucosuria. This fasting-like effect, not seen with other antihyperglycemic drugs, triggers nutrient deprivation pathways, including stimulation of gluconeogenesis and ketogenesis to promote cellular homeostasis [21–23]. The gluconeogenesis and ketogenesis are regulated by endogenous nutrient deprivation sensors silent information regulator T1, proliferator-activated receptor gamma coactivator 1-alpha and fibroblast growth factor 21, which are known to exert cardioprotective effects in experimental models [23]. The aforementioned benefit occurs to be mediated by alleviating oxidative stress and promoting autophagy. This degradative pathway plays a crucial role in lysosome-dependent disposing of dysfunctional cellular components that constitute a significant cause of cell damage [13, 22, 23].

On the other hand, clinical trials have not shown a reduction in HF events related to metformin stimulation of the adenosine monophosphate–activated protein kinase, a known sensor for nutrient deprivation that does not induce ketogenesis. Therefore, the main focus of the positive cardiovascular and renal effects of SGLT2 inhibition is the boost in ketone bodies production as a more potent fuel source for mitochondria compared to free fatty acids [1, 5, 12, 13, 23, 24]. The rapid-onset renal and cardiovascular benefits demonstrated in the trials' outcome remain consistent with this very elegant metabolic theory [13, 18, 19, 25].

It has also been postulated that SGLT2i directly inhibit Na+/H+ exchanger (NHE) 1, leading to reduced sodium and calcium cytoplasmic levels and to increase in mitochondrial calcium levels, thus restoring mitochondrial function and stimulating energy production [26, 27].

Solini et al. [28] demonstrated the influence of dapagliflozin on the expression of miRNAs related to HF pathophysiology: upregulation of miR30e-5p and downregulation of miR199a-3p. Moreover, SGLT2 inhibition preserves renal vasodilating capacity. The aforementioned effects operate independently of the diuretic and blood pressure-lowering properties of dapagliflozin [29]. They also showed a significant dapagliflozin-induced rise in magnesium concentrations, which are known to be inversely associated with risk for coronary heart disease and HF deaths. Therefore, this might contribute to the cardiovascular protection exerted by SGLT2i [28, 30].

Administration of SGLT2i is associated with the acute decrease in creatinine clearance related to resetting macula densa tubuloglomerular feedback. Inhibition of proximal sodium absorption delivers an excess of sodium to the macula densa, which acts as a trigger releasing vasoconstrictive molecules. This mechanism results in vasoconstriction of the glomerular afferent arterioles reduces glomerular filtration rate and protects against the harmful impact of blood pressure increases and fluctuations on the glomerular capillaries located downstream [31]. Nevertheless, the renoprotective effects that SGLT2i exert cannot be easily explained only by their actions to lower blood glucose, blood pressure, or glomerular filtration pressures.

In the cardiovascular outcome trials increase in hematocrit was observed, but the mechanism of this phenomenon was not clearly explained [18, 19]. In the EMPA-HEART study, empagliflozin use was associated with an increase in erythropoietin level. Several mechanisms at the kidney level may be responsible for this effect [32]. The rise in hematocrit suggests that SGLT2i influence hypoxia-inducible factors (HIFs; specifically, HIF-1α and HIF-2α). This property could be the underlying reason for their ability to prevent nephropathy from progressing [33]. Defective nutrient deprivation signaling, oxidative and endoplasmic reticulum stress as well as renal hypoxia are all features of type 2 diabetes. These conditions tend to cause

Table 1. Multidirectional mechanisms of sodium-glucose co-transporter 2 (SGLT2) inhibitors activity in various clinical indications.

Clinical setting	Heart failure	Type 2 diabetes	Chronic kidney disease
Pathophysiological effect	Increased urinary sodium excretion, increased osmotic diuresis, decreased plasma and interstitial fluid volume, decreased preload, decreased arterial stiffness, decreased afterload, improved autonomic balance, decreased inflammation, decreased plasma B-type natriuretic peptide, increased plasma Mg	Decreased glucose reabsorption, increased insulin sensitivity, decreased HbA1c, decreased inflammation, whole body energy deficit, weight loss	Decreased urinary albumin excretion, decreased plasma B-type natriuretic peptide, decreased inflammation, preserved renal vasodilating capacity, reduced glomerular hypertension, improved renal function, attenuated diabetes-induced tubulointerstitial fibrosis

a shift in HIF-1α/HIF-2α activities ratio through simultaneous HIF-1α activation and HIF-2α suppression. The resulting balance change stimulates profibrotic and proinflammatory pathways in both tubular and glomerular cells [33]. Several small studies with SGLT2i confirmed a slight reduction in serum inflammatory markers: high sensitivity C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and interferon-gamma, which was summarized by Bonnet and Sheen [29]. Moreover, SGLT2 inhibition with dapagliflozin was shown to slow down the progression of diabetes-associated renal tubulointerstitial fibrosis by improving hyperglycemia-induced activation of the signal transducer and activator of transcription-1/transforming growth factor-beta 1 pathway [34]. Thus, reduction of inflammation can be considered as another mechanism explaining the beneficial effect of SGLT2i at the kidney and myocardium levels.

The summary of mechanisms of SGLT2i in various clinical settings is presented in Table 1.

Sodium-glucose co-transporters inhibitors

Several SGLT2i have been developed, including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, sotagliflozin, and tofogliflozin; however, only a few of them have been tested in large-scale, long-term, randomized clinical trials. Only dapagliflozin and empagliflozin were evaluated in patients with HF regardless of a diabetes diagnosis [35–37]. Both these agents have shown high efficacy in reducing the primary outcome defined as a composite of worsening HF or cardiovascular death. Cardiovascular mortality and all-cause mortality were significantly decreased regardless of a diabetes diagnosis only with dapagliflozin [35], while in patients with type 2 diabetes, only with empagliflozin [12]. Treatment with empagliflozin and dapagliflozin was safe and well tolerated, resulting in excellent adherence to medication — a key factor in the long-term treatment of patients with chronic diseases [38–49].

Based on the results of clinical trials, McMurray and Packer [50] proposed a new algorithm for the sequencing of foundational treatments in HF patients with reduced ejection fraction. The 3-step algorithm should be applied in a patient in whom clinical euvolemia has been achieved with diuretics. The treatment should be started with simultaneous initiation of treatment with a beta-blocker and an SGLT2i (step 1); the addition of sacubitril/valsartan (step 2); and the subsequent addition of an mineralocorticoid receptor antagonists (step 3). The proposed approach is expected to maximize the likelihood that highly effective therapies will be implemented in a manner that rapidly prevents deaths and hospitalizations and enhances the tolerability of concurrently or subsequently administered treatments [50].

Conclusions

Due to the complex and multidirectional mechanism of action of SGLT2i, this originally antidiabetic group of drugs has been successfully used to treat patients with HF and subjects with chronic kidney disease. Moreover, their therapeutic potential seems to be even wider than the indications studied so far.

Conflict of interest: Jacek Kubica, Aldona Kubica, Ryszard Gellert, Maciej Lesiak: personal fees from

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