Effect of sodium-glucose co-transporter inhibitors on blood pressure values. A new class of diuretic drugs?

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Abstract

New sodium-glucose co-transporter (SGLT 2) inhibitors are already widely used in patients with diabetes mellitus and in patients with heart failure. From the beginning of their use, it has been noticed that they slightly but statistically significantly lower both systolic blood pressure (SBP) and diastolic blood pressure (DBP). The antidiabetic activity of these drugs is based on the inhibition of the reabsorption of glucose and partially sodium in the renal tubules, which leads to an increase in the amount of urine excreted. Most likely, increased diuresis is responsible for the drop in blood pressure (BP). So far, numerous meta-analyses confirming the reduction of BP in diabetic patients have already been published, for both office BP and home BP, twenty-four hour BP and ambulatory central blood pressure. The action of SGLT 2 inhibitors, after a single administration, extends over 24 hours and there are already the first successful attempts to use them in hypertension in the course of diabetes mellitus with obstructive sleep apnea. The action of SGLT 2 inhibitors is pleiotropic and, apart from the diuretic effect, they slightly reduce the patient's weight, reduce the activity of the sympathetic nervous system, restore the normal function of the endothelium, increase uric acid excretion, and reduce blood vessel stiffness. All these factors are responsible for the drop in BP. These favorable properties of SGLT 2 inhibitors indicate that these drugs will be increasingly used, probably not only in diabetes.

Key words: SGLT2 inhibitors; blood pressure; blood vessel stiffness; activity of the sympathetic nervous system; endothelium

Arterial Hypertens. 2022, vol. 26, no. 2, pages: 60–66
DOI: 10.5603/AH.a2022.0010

Introduction

Hypertension is still one of the most common causes of death in the world [1, 2]. Such a high mortality is largely due to insufficient compliance between the doctor and the patient. The introduction of single-pill combinations of two or more blood pressure-lowering drugs significantly improved the therapy, but in about 10% of patients with arterial hypertension it is still not possible to achieve the normalization of BP despite the simultaneous use of 3 drugs lowering BP, including a diuretic in full doses [3]. For many years, the arsenal of antihypertensive drugs has not increased with new, effective preparations, unlike in other branches of medicine, e.g. oncology or diabetes. It can be hoped that the intensive research will be successful in introducing a new class of antihypertensive drugs. In

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the meantime, it is worth becoming interested in drugs used in indications other than hypertension, drugs that additionally show a slight but statistically significant antihypertensive effect. Such drugs are the SGLT 2 inhibitors, which are successfully used in diabetes and cardiology [4, 5].

Since 2008, manufacturers of new antidiabetic drugs have been obliged by the American Food and Drug Administration (FDA) to additionally test them for cardiological safety. Surprisingly, large studies have shown that SGLT2 inhibitors, new antidiabetic drugs, not only are not dangerous to the cardiovascular system, but also prevent more frequent hospitalizations for heart failure. Compared to placebo, empagliflozin has been shown to significantly reduce the endpoint of death from cardiovascular causes and non-fatal infarction and stroke [5]. Further studies showed that similar class effects were also shown by other SGLT2 inhibitors; in particular, they reduce hospitalizations due to heart failure by 30%, regardless of the presence of cardiovascular diseases and the severity of heart failure [5, 6]. In the EMPEROR study, it was decided to investigate the effectiveness of SGLT2 inhibitors in nondiabetic patients with heart failure (HFREF < 30%). In this study, a significantly reduced percentage of hospitalizations and deaths from cardiovascular causes as well as a slower progression of heart failure were observed. In 2021 year, the results of the EMPEROR Preserved study were published, in which patients with chronic heart failure and a preserved ejection fraction (EF > 40%) were treated [7]. As is well known, drugs successfully used in patients with chronic heart failure and a reduced ejection fraction are not effective or much less effective in patients with preserved ejection fraction. Empagliflozin also unexpectedly reduced the hospitalization rate of these patients by 29% regardless of the presence of diabetes. It has also been shown that treatment with PGLT2 inhibitors leads to a reduction in left ventricular mass [8].

SGLT2 inhibitors are drugs with pleiotropic action. They lower blood glucose levels and have cardiovascular and nephroprotective effects. By lowering the hydrostatic pressure in the glomerulus they reduce the progression of nephropathy. Interestingly, they reduce the interstitial volume to a greater extent than the intravascular volume, so they do not lead to systemic hypoperfusion [9]. Due to their unique action, they do not lead to compensatory adrenergic activation. As a result of glycosuria, calories are lost and body weight is reduced by about 2–3 kg [10]. By acting as a diuretic, they increase the amount of urine excreted by 300 ml/day. One of the factors that are likely to reduce the risk of cardiovascular disease is a slight but statistically significant drop in blood pressure. This effect of SGLT2 inhibitors has been described by many researchers and has been confirmed in several meta-analyses [11–13]. Almost all the observations were made in diabetic patients, while some studies concern patients with heart failure or chronic kidney disease without diabetes. They concerned both systolic and diastolic pressure. Recently, a study was published discussing the influence of empagliflozin on BP values in 45 healthy volunteers. As expected, the drug significantly lowered office blood pressure and twenty-four hour BP [14].

Influence of SGLT2 inhibitors on office blood pressure

One meta-analysis by Vasilakou at al. investigating changes in BP with SGLT2 inhibitors reported mean reduction in SBP of –3.77 mm Hg versus placebo and corresponding reduction in DBP was –1.75 mm Hg [11]. Another meta-analysis reported decreases in SBP and DBP during SGLT2 inhibitor therapy compared with placebo/control of –2.45 mm Hg and –1.46 mm Hg respectively [12]. Khan et al. showed a greater drop in blood pressure after using canagliflozin. It was 4.4 0/1.68 mm Hg [15].

Influence of SGTL2 inhibitors on twenty-four hour BP

Two further meta-analyses concerned the behavior of arterial pressure during SGLT2 inhibitor therapy, where 24-hour BP was measured. The first study reported a decrease in 24-hour SBP and DBP of –3.76 and –1.83 mm Hg, respectively, compared with placebo [13]. Similar magnitude of BP reduction with SGLT2 inhibitors versus placebo was found in second meta-analysis [16]. The SACRA study, in which 12 weeks of empagliflozin treatment resulted in a 9.5/7.7 mm Hg decrease in BP compared to placebo, was not included in both meta-analyses [17]. All reported pressure drops after treatment with SGLT2 inhibitors were statistically significant.

Influence of SGTL2 inhibitors on home BP

Japanese researchers conducted a study assessing blood pressure values in home measurements after administration of canagliflozin [18]. They noted a decrease in systolic blood pressure of 5.23 mm Hg

vs. 1.04 mm Hg after placebo administration, morning home SBP –6.82 *vs.* 1,26 mm Hg, evening home SBP –8.74 *vs.* 2,36 mm Hg (p = 0.012).

The influence of ethnic differences on the drop in BP after SGLT2 inhibitor treatment

Asian population tends to develop diabetes mellitus at an earlier age than White population. Diabetic complications are also more common in the Asian population [19]. The studies conducted so far indicate a greater reduction of blood pressure during treatment with SGLT2 inhibitors in a group of Asians than in populations in Europe and the United States. More frequent occurrence of hypertension and more frequent complications of this disease are also observed among African-Americans. SGLT2 inhibitors produce a greater daily blood pressure drop in this population than in Whites but less than in Asians [20]. Only the nighttime drop in blood pressure is comparable to that of Asians, and much greater than that of Whites [20]. Greater BP reduction was observed in people with higher body weight and in people with higher blood pressure at the beginning [20]. Such a drop in blood pressure was recorded both in the office BP and in the 24-hour BP.

SGLT 2 inhibitors in the reduction of arterial hypertension in the course of obstructive sleep apnea

Obstructive sleep apnea is common in people with diabetes. The coexistence of these two factors is estimated at up to 86% in patients with type 2 diabetes [21]. Treatment with canagliflozin at a dose of 100 mg/day reduced blood pressure and at the same time decreased the apnea/hypopnea index from 31 to 18.8 apnea events/h [22]. After 24 weeks of treatment, dapagliflozin in combination with metformin reduced somnolence, as measured by the Epworth Sleepiness Scale score and improved minimal oxygen saturation [22, 23].

Georgianos and Agarwal compared in their meta-analysis the hypotensive effect of SGLT2 inhibitors and hydrochlorothiazide on blood pressure values [16]. The decrease in SBP in this meta-analysis after SGLT2 inhibitors was 3.62 mm Hg and the decrease in DBP was 1.7 mm Hg in 24-hour recording. According to the authors of this study, very similar blood pressure reduction results are also observed after a low dose of hydrochlorothiazide.

Mechanisms of BP lowering by SGLT inhibitors

So far, this mechanism is not fully understood. It is most likely multifactorial. Its diuretic effect is believed to be the most important factor. The sodium-glucose cotransporter 2 inhibitor molecule combines with a single glucose molecule and one sodium ion and transports them to the proximal part of the renal tubule. There, glucose is excreted and sodium reabsorption is inhibited. The amount of sodium excreted and the volume of urine increase. Many studies have shown an increase in urine volume from 110 mL/day to 470 mL/day [23]. Moreover, experimental studies have shown that SGLT2 inhibitor therapy reduces the increase in blood pressure in the course of the high-sodium diet [24]. At the same time, no increased heart rate is observed, which suggests the inhibitory effect of SGLT2 inhibitors on the sympathetic nervous system. In addition, SGLT2 inhibitors reduce body weight, reduce blood vessel stiffness, increase uric acid excretion and have a beneficial effect on the vascular endothelium. Increased uric acid excretion following the administration of SGLT2 inhibitors has also been shown in healthy subjects [25]. Reduced uric acid levels are associated with a reduced risk of emerging hypertension [26]. In turn, the ketogenic hypothesis assumes that SGLT2 inhibitors increase the concentration of β-hydroxybutyrate in the blood serum, and this compound reduces blood pressure [27]. Weight loss in patients using SGLT 2 inhibitors is relatively small, usually around 2 kg. Previous studies have shown that body weight reduction of 1 kg lowers systolic blood pressure by about 1 mm Hg.

Katakami et al. in UTOPIA study researched the effect of tofogliflozin treatment on vascular stiffness assessed by pulse wave velocity in diabetic patients [28]. This randomized, prospective, 104-week study included 80 patients treated with this SGYL2 inhibitor and 74 conventionally treated patients. This SGLT2 inhibitor therapy significantly reduced the pulse wave velocity from 184 cm/sec to 109 cm/sec ($p < 0.005$). The reduction in vascular stiffness after treatment with SGLT2 inhibitors was independent of the subjects' body weight, percentage of glycated hemoglobin, cholesterol triglycerides, baseline systolic blood pressure, smoking, and other drugs used. An important factor influencing vascular stiffness is blood pressure. The authors of this study divided all the subjects treated with tofogliflozin into two subgroups depending on the changes in blood pressure during the treatment of the tested SGLT2 inhibitors. The first subgroup included patients with

a drop in blood pressure, and the second subgroup included patients with unchanged blood pressure or a slight increase in blood pressure. The authors observed a reduction in vascular stiffness only in the second group of patients. Thus, the beneficial effect of SGLT2 inhibitor cannot be explained only by the drop in blood pressure. Previously, other authors have already shown a decrease in vascular stiffness after treatment with empagliflozin, dapagliflozin and canagliflozin. Several researchers observed different results [29]. Patoulias et al., who summarized the conclusions of these studies, assessed that the controversial results can only be explained by subsequent studies with more patients [30]. Many factors can increase vessel stiffness. These include insulin resistance, hyperglycemia, chronic inflammation, oxidative stress, and increased activity of the renin-angiotensin-aldosterone system. SGLT2 inhibitors have a positive effect on many of the above-mentioned factors, but based on currently available studies, it is not possible to assess their individual contribution to the development of vessel stiffness.

A drop in central arterial pressure was demonstrated by Eirini et al. during treatment with dapagliflozin [31]. In this study 85 diabetic patients were included and divided into a subgroup treated for 6 weeks with SGLT2 inhibitor and a subgroup without this drug. Both subgroups did not differ in age, gender, BMI index, incidence of arterial hypertension and dyslipidemia. Antidiabetic and antihypertensive drugs (except dapagliflozin) were also similar in both study groups. After the end of the study, the peripheral arterial pressure assessed by ABPM method decreased from 129/77 to 123/75 mm Hg, heart rate did not change. Central systolic blood pressure decreased from 117.4 to 113.3 mm Hg, central diastolic blood pressure dropped from 78.9 to 77.3 mm Hg, and the pulse wave velocity decreased from 8.82 to 8.66 m/sec. In contrast to patients treated with SGLT inhibitors, in the control group, these parameters did not change significantly. A decrease in central arterial pressure was also observed by Striepe et al. in diabetic patients after treatment with empagliflozin [32].

Reduction of arterial pressure and plasma volume by stimulating the sympathetic nervous system increases the heart rate. On the other hand, the fact that no increase in heart rate is observed after the administration of SGLT2 inhibitors raises the suspicion that these drugs inhibit the activity of this system [33]. An interesting observation is presented by Sano M. who in a clinical study in patients with diabetes and increased heart rate showed not only no change in the heart rate, but also a decrease in heart rate after treatment with luseogliflozin [34]. Inhibition of the sympathetic system in the tissues of the heart and kidneys after the administration of dapagliflozin was demonstrated in an animal experiment by Matthews et al. [35]. Similarly, the results of using a different research methodology were obtained by Nguyen et al. [36]. In their opinion, however, the inhibition of the autonomic sympathetic system after the administration of dapagliflozin occurs through the action on the central nervous system. Next work was presented by Wan et al. who observed in obese mice fed a high-salt diet an increase in blood pressure, also at night, and an abnormal circadian rhythm of the sympathetic nervous system [37]. The administration of SGLT2 inhibitors did not change the heart rate; it normalized the circadian rhythm of blood pressure and the sympathetic nervous system. In clinical trials, Jordan et al. used microneurographic assessment in diabetic patients before and after SGLT2 inhibitor treatment [38]. They investigated muscle sympathetic nerve activity (burst frequency, burst incidence and total MSNA) after 4 days of empagliflozin treatment in 22 patients with type 2 diabetes. Despite a significant increase in urine output, they did not show significant changes in the activity of the sympathetic system. In their other studies, after administering a diuretic they always observed an increase in the activity of this system. Inhibition of the sympathetic nervous system is also achieved after the denervation of the renal arteries. In patients treated with this method, the reduction in blood pressure is only slightly greater than with SGLT 2 inhibitors [39].

According to many researchers, the beneficial effect of SGLT2 inhibitors on the reduction of cardiovascular mortality in patients with diabetes cannot be explained only by a reduction in blood glucose levels, weight loss or a reduction in blood cholesterol levels. In their opinion, there is another important mechanism responsible for this. They suggest that the improvement in endothelial function may explain the therapeutic effects of these drugs [40–42]. Recent experimental and clinical studies confirm the important role of the influence of SGLT2 inhibitors on endothelial function. Among others, studies in mice and rabbits showed vasodilation of the aorta after administration of dapagliflozin or empagliflozin [43]. Subsequent studies have documented the reduction of oxidative stress and chronic inflammation. These changes significantly improve the endothelial function [40]. However, clinical results of endothelial function tests by flow mediated dilatation (FMD) technique are contradictory. Solini et al. showed no changes in this

parameter after four-week treatment with dapagliflozin [44], but other authors observed a significant improvement in a randomized study of patients with diabetes and atherosclerotic complications [45]. A similar effect was observed by the next authors in patients with type 1 diabetes [46]. They showed improvement of endothelial function through the increased excretion of nitric oxide dilates the vessels and lowers blood pressure. In the studies of Park et al., angiotensin II increased the activity of SGLT2, which by increasing vascular cell adhesion molecule (VCAM) and monocyte chemoattractant protein-1 (MCP-1) decreased the activity of endothelial nitric oxide synthase (ENOS) and impaired endothelial function. SGLT-2 inhibitors restored normal endothelial function [47].

An additional explanation for BP reduction by SGLT2 inhibitors is the local inhibition of the RAAS secondary to increased delivery of sodium to the juxtaglomerular apparatus. This increased sodium delivery to the macula densa and resulted in production of the potent vasoconstrictor adenosine, afferent arteriolar vasoconstriction, and decreased renal blood flow. This may be related to a postulated renoprotective role of SGLT2 inhibitors [48] Finally SGLT 2 inhibitors attenuate systemic oxidative stress [48].

SGLT2 inhibitors are safe drugs. The most common complication that occurs after the use of these drugs is infection of the urinary tract with bacteria or fungi. This infection is favored by a large amount of glucose in the urine. An increased risk of amputation of the toe, foot, and even the entire lower limb was seen with canagliflozin in the CANVAS study [49]. This SGLT2 inhibitor also increased the frequency of bone fractures, although more data are necessary before drawing definite conclusions. Diabetic ketosis has been rarely observed. SGLT2 does not affect Langerhans islet beta cells. Hypoglycemia is practically absent [50].

SGLT 2 inhibitors used in diabetic patients have a hypotensive effect comparable to the low dose of hydrochlorothiazide. In contrast to the latter, they additionally reduce the activity of the sympathetic system, do not cause electrolyte disturbances and improve the function of the endothelium. Added to beta-blockers, convertase inhibitors, sartans and calcium antagonists, they exert an additive effect, but no additive effect after thiazides and loop diuretics [51]. They have a stronger antihypertensive effect in patients with initially higher blood pressure and in obese people. They do not lower blood pressure in patients with heart failure and low blood pressure at baseline, very rarely causing symptomatic hypotension [52]. Studies are underway in people without diabetes, mainly in patients with mild hypertension or in prediabetes.

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