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Research Article

# Effect of Sglt2 Inhibitors on Hypretension, in Diabetic and Non-Diabetic Patients

*Shalabh Jauhari[1], Shatakshi Rai[2] and Reenoo Jauhari[3*]*

[1]*Department of Microbiology, Government Doon Medical College, India*

[2]*Department of Pharmacy Practice, School of Pharmaceutical Sciences, India*

[3]*Department of Pharmacy Practice, School of Pharmacy, Graphic Era Hill University, India*

## Abstract

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and Gestational Diabetes Mellitus (GDM) is still the most accepted classification and adopted by ADA. Type 1 Diabetes Mellitus is a result of impaired insulin secretion, Type 2 Generally, a Negative feedback mechanism is there that controls homeostasis of our body, but there is no negative feedback mechanism for the reabsorption of glucose from the proximal renal tubule. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the drugs that control the reabsorption of glucose from the proximal renal tubule. It has become clear that SGLT2 inhibitors not only improve the blood glucose level, but also show cardiovascular and renal protective effects irrespective of the reduction of blood glucose in patients with Type 2 Diabetes Mellitus (T2DM). There is an activation of sympathetic nervous system which causes the development of hypertension in Type 2 Diabetes Mellitus (T2DM) patients. In this review we will discuss about various cardiovascular protection done by SGLT2 Inhibitors in both diabetic and non-diabetic patients.

**Keywords: Type 2 Diabetes Mellitus (T2DM); Sodium-Glucose cotranspoter-2 (SGLT2) inhibitors; Hypertension; Cardiovascular**

## Introduction

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and Gestational Diabetes Mellitus (GDM) is still the most accepted classification and adopted by ADA [1]. Type 1 Diabetes Mellitus is due to impaired insulin secretion, Type 2 Generally, a Negative feedback mechanism is there that controls homeostasis of our body, but there is no negative feedback mechanism for the reabsorption of glucose from the proximal renal tubule. Sodium–Glucose Cotransporter-2 (SGLT2) inhibitors are the drugs that control the reabsorption of glucose from the proximal renal tubule. It has become clear that SGLT2 inhibitors not only improve the blood glucose level, but also show cardiovascular and renal protective effects irrespective of the reduction of blood glucose in patients with Type 2 Diabetes Mellitus (T2DM). There is an activation of sympathetic nervous system which causes the development of hypertension in Type 2 Diabetes Mellitus (T2DM) patients. Diabetes Mellitus is *via* peripheral actions of insulin and Gestational Diabetes is a form of T2DM but occurs in pregnant women [2].

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***Corresponding author:** Reenoo Jauhari, Department of Pharmacy Practice, School of Pharmacy, Graphic Era Hill University, Clement Town, Dehradun, India, Tel: +91-8881722280; E-mail: reenoojauhari1309@gmail.com

Hypertension (HTN) is present in more than 50% of patients with Diabetes Mellitus (DM) and contributes significantly to both micro and macrovascular disease in diabetes. DM and HTN share several pathophysiologic mechanisms including: inappropriate activation of the Renin Angiotensin Aldosterone System (RAAS), oxidative stress secondary to excessive production of Reactive Oxygen Species (ROS), inflammation, impaired insulin-mediated vasodilatation, increased Sympathetic Nervous System (SNS) activation, dysfunctional innate and adaptive immune responses and abnormal renal handling of sodium [3-6].

### Pharmacokinetics and pharmacodynamics of SGLT2 inhibitors

SGLT2 Inhibitors are independent of pancreatic endocrine secretion and can be used in monotherapies or can be co-administered with clinically prescribed antidiabetic agents [7-9]. The pharmacokinetic of SGLT2 Inhibitors are:

- Bioavailability of the drugs varies from 60% to 80%.
- Therapeutic dose may range from 100 mg-300 mg (Canagliflozin), 5 mg-10 mg (Dapagliflozin), 10 mg-25 mg (Empagliflozin) and 25 mg-50 mg (Ipragliflozin).
- Drug is eliminated *via* urine and feces in an inactive metabolite form.
- The drugs are metabolized *via* Glucuronidation reaction.
- Plasma protein binding is 90%-99%.

The SGLT2 are responsible for the reabsorption of 90% glomerular glucose and its inhibitors can only suppress up to 30%-50% of total. As the drugs are actively eliminated/reabsorbed from the same site, thus reducing the blocked transporters along the proximal tubule [10].

### SGLT2 inhibitor and hypertensive effect

There is not a single mechanism that can explain the favorable

effects of SGLT2 Inhibitors on cardiovascular outcomes. There is an indirect improvement of cardiac functions by the inhibition of SGLT2 which occurs *via* natriuresis followed by reduction of volume overload. Several different theories have been proposed to explain the profound salutary effects of SGLT2 inhibitor on cardiovascular outcomes. It is suggested that inhibition of SGLT2 decreases ventricular overload through its diuretic effects thereby reducing blood pressure [11].

Recently in EMPA-REG OUTCOME trial, it was reported that the SGLT2 inhibitor empagliflozin significantly reduce the rate of primary composite cardiovascular outcome and also prevent death from any cause in patients with T2DM which are at risk of developing a cardiovascular disease. This was the first study which reported that an antidiabetic agent reduce mortality in patients with T2DM. The additional use of SGLT2 inhibitors significantly reduced the onset and worsening of nephropathy in the subgroup analysis of the EMPA-REG OUTCOME trial [12,13].

Zhao Li conducted a retrospective observational study both *in vivo* and *ex vivo* in diabetic and non-diabetic groups with SGLT2 Inhibitors (Canagliflozin, Dapagliflozin and Empagliflozin) and the results suggested that the drugs are cardioprotective irrespective of the diabetic status. Inhibition of SGLT2 protects the heart through natriuresis, metabolic shift, improved Ca2+ handling, hypertension and reduction of cardiac fibrosis. So, the study suggested that SGLT2 Inhibitors can also be given to non-diabetic patients as it had beneficial effects in them [14].

Kario et al. [15] conducted a randomized, placebo-controlled SACRA Study (SGLT2 inhibitor and Angiotensin Receptor Blocker (ARB) Combination Therapy in Patients with Diabetes and Uncontrolled Nocturnal Hypertension) which investigated changes in Blood Pressure (BP) with empagliflozin plus existing antihypertensive therapy in 2018. There was a 12 week study conducted in which one group was given a placebo drug and another group was given empagliflozin 10 mg. It was observed that there was a reduction in the night time BP. The numeric difference observed in placebo was (-4.3 mmHg) and the reduction from baseline with empagliflozin was (-6.3 mmHg). So, the study concluded that the use of SGLT2 Inhibitors has a beneficial effect in lowering blood pressure in T2DM patients with hypertension [15].

SGLT2 inhibitors reduce central sympathetic overactivity, probably by suppressing renal afferent signaling to the brain. They decrease sympathetic outflow from the brain to the kidney and alters the pressure-natriuresis relationship so that the kidneys excrete more sodium and water at a given pressure, thereby improving fluid retention. It may also suppress the Rennin Angiotensin System (RAS) thereby helping in lowering the blood pressure and providing cardiovascular protective effect [16]. A study of SGLT2 Inhibitors (dapagliflozin) was conducted the results were analyzed in a trial known as DECLARE-TIMI 58, in which the T2DM patients were given dapagliflozin and their effect on cardiovascular outcome was studied. It is a known fact that dapagliflozin causes blood pressure reduction. A phase III study was conducted and the effect of dapagliflozin on blood pressure was studied on the T2DM patients with hypertension. The results of the study were that there was a difference of -4.28 mmHg between the group on dapagliflozin and a renin-angiotensin-aldosterone system blocker and the group on an antihypertensive alone. It is also suggested that the use of dapagliflozin reduces diabetic nephropathy [17,18].

As we already know that SGLT2 inhibitors works by reducing blood pressure and restores tubuloglomerular feedback. Kim et al. [19] conducted research in 2019 in which he studied the effect of empagliflozin in which he demonstrated that the use of SGLT2 Inhibitors was effective at controlling salt-sensitive hypertension, which was induced by renal mass reduction in non diabetics. The study concluded that there is upregulation of HIF-1α (Hypoxia inducible factor, a complex protein which helps in body's response to low oxygen concentration) which contributes to the protective effects of SGLT2 inhibitors on blood pressure, and empagliflozin exerts anti-inflammatory action in non-diabetic kidney disease as well [19].

Even though SGLT2 inhibitors are not approved as antihypertensive agents, there are various trials which reported SGLT2 inhibitors reduces systolic and diastolic blood pressure by 3 mmHg-7 mmHg and 2 mmHg, respectively [20,21]. Blood pressures reduction is independent of the diseased status, so, it is interesting to note that blood pressure reduction with SGLT2 Inhibitors may occur by inhibiting SGLT2 receptors which prevent reabsorption of filtered glucose at the proximal convoluted tubule and leads to insulin-independent glycosuria which results in weight reduction, diuretic effect and reduction of various sympathetic activities. The drug also reduces the arterial stiffness, thus also suggesting to vascular effects [22,23]. The effects on blood pressure are not restricted to daytime, as nocturnal blood pressure is also decreased, which is a predictor for cardiovascular and renal disease progression [24,25]. SGLT2 Inhibitors might also improve cardiac preload by lowering plasma volume and causing osmosis and natriuretic diuresis, secondary to urinary sodium and glucose excretion. These processes can beneficially influence kidneys and heart thereby helping in blood pressure reduction. Therefore, the use of SGLT2 Inhibitors in non-diabetic kidney disease patients is also beneficial [26,27].

Recently a DAPA-HF trial was published in which the effect of SGLT2 Inhibitor (dapagliflozin) was studied in both diabetic and non-diabetic groups. It was found that there was beneficial effect on cardiovascular outcomes, decreased heart rate and there was some decline in glomerular filtration rate in patients which were diabetic and non-diabetic [28]. Tikkanen et al. [29] also investigated the effectiveness of the empagliflozin on blood pressure using 24 hour ambulatory blood pressure monitoring. It was a randomized study on 800 type 2 diabetic patients over 60 years of age. The subjects taken were either normotensive (<140/90 mmHg) or had stage 1 hypertension (≥ 140/90 or <160/99 mmHg). The dose given was either 10 mg daily, 25 mg daily or placebo and at the same the HbA1c levels were also analyzed over 12 weeks study. The end point of the study was the change in the mean systolic blood pressure as there was a differenced of 4 mmHg from the placebo. There was a significant reduction of both systolic and diastolic blood pressure, 4/2 mmHg at 25 mg empagliflozin as compared to the placebo. As the drugs have salutary effects (i.e., blood pressure-lowering and weight-reducing effects) and are safe as they are not associated with hypoglycemia except when given in combination with insulin or sulfonylurea so furthers studies should be done to check the beneficial effect of these classes of drugs [29].

Heart et al. [30] conducted a study on neurogenic hypertensive mouse model, known as the Schlager (BPH/2J) interaction between sympathetic hyperactivity and SGLT2 regulation was analyzed. The study was carried out for 18 to 20 weeks on non-diabetic mouse and the results were then analyzed. The results of the study concluded that

there was reduction in blood pressure as well as glucose homeostasis was also maintained by the use of SGLT2 Inhibitor dapagliflozin. Further the study also demonstrated that dapagliflozin also controls the elevation of both systolic and diastolic blood pressure in mouse. It is essential that future studies aim to assess whether SGLT2 inhibition will also result in sympatho-inhibition in human hypertensive subjects [30].

Recently there are various studies which are going on to check the benefits of SGLT2 Inhibitors on cardiovascular outcomes independent of the patients having diabetes.

## Conclusion

SGLT2 Inhibitors significantly reduce HbA1c levels but also helps in reducing systolic blood pressure in patients with T2DM. Generally, canagliflozin, dapagliflozin and empagliflozin are the drugs which are used in the studies to determine the beneficial effect of SGLT2 Inhibitors in both T2DM and non-diabetic patients. There is some amount of clinical data available which provides information regarding the use of SGLT2 Inhibitors in T2DM patients with hypertension as the drug also act as the cardioprotective agent, increases diuresis, maintain glucose homeostasis by inhibiting its reabsorption from the proximal tubule thereby reducing blood pressure. There are still various clinical trials on run to provide the beneficial effect of SGLT2 Inhibitors in non-diabetic patients, though various pre-clinical studies on animals have been don which reported the beneficial effect of SGLT2 Inhibitors in non-diabetic groups. Its beneficial effects in humans are yet to be done in clinical trials. But there are various studies which demonstrated that the SGLT2 Inhibitors also have a significant cardioprotective property and nephroprotective property irrespective of its antidiabetic action.

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