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*Case report*

# Can SGLT2 Inhibitors be a Good Option in the Management of Resistant Hypertension in Diabetic Hypertensive Patients?

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**Abstract**

67-year-old diabetic hypertensive female patient presented with severe headache and severe hypertension. Carvedilol and spironolactone were added, because her blood pressure could not be controlled with 3 antihypertensive drugs, one of which was diuretic. After the addition of SGLT-2 inhibitor, blood pressure values were found to be around 150-140/90 mmHg. Features of this case supports the possible role of SGLT2-inhibitors in resistant hypertensive and diabetic patients in appropriate clinical conditions.

**Keywords:** Resistant hypertension, SGLT2-inhibitors, Type 2 Diabetes Mellitus

## Introduction

Resistant hypertension is defined as inability to control blood pressure despite optimum doses of 3 different antihypertensive drugs (one of which is a diuretic) or to provide adequate blood pressure control with 4 or more different antihypertensive drugs [1]. Despite advances in the diagnosis and treatment of resistant hypertension, there are still significant challenges and unmet needs for appropriate diagnosis and management [1]. The incomplete understanding of the precise pathophysiological mechanisms of resistant hypertension has hampered efforts to identify the optimal treatment approaches [2]. More research is needed on new treatment approaches, including different perspectives to treat resistant hypertension. Despite the widespread use of antihypertensive therapy, a significant portion of the hypertensive population remains uncontrolled, making it rational to test alternative approaches in patients with refractory hypertension [3]. On the other hand, considering the significant cardiovascular mortality burden of diabetic refractory hypertensive cases, there is a need for new treatment approaches that reduce blood pressure and improve cardiovascular outcomes [4]. In addition to other antihypertensives, SGLT2 inhibitors that reduce blood pressure as well as improve cardiovascular and renal morbidity and mortality may be promising in diabetic patients with resistant hypertension in favorable clinical conditions [5].

## Case

A 67-year-old female patient with a diagnosis of diabetes and hypertension was admitted to the internal medicine clinic due to gradually increasing headaches and accompanying high blood pressure measured for the last two months. On physical examination, blood pressure was 220/110 mmHg, and pulse was 86/minute. Heart sounds were rhythmic, additional sounds and murmurs were not heard. Electrocardiography was in normal sinus rhythm and there were signs of left ventricular hypertrophy. Her body weight was 62 kilograms, her height was 165 cm, and her body mass index was 22.8 kg/m$^2$. There were no significant findings in the history of the patient, except for a history of hysterectomy due to menometrorrhagia 10 years ago. The patient, who described panic attacks from time to time, did not receive any treatment for this. During examination, the patient stated that she had sleep problems. Salt restriction and a diabetic diet were initiated. Intensive insulin therapy, which she was still using for diabetes, was continued. In laboratory tests, fasting blood glucose was 151 mg/dl, creatinine 0,8 mg/dl, urea: 57 mg/dL, LDL cholesterol value 129 mg/dl, HbA1c level 7.8%, and eGFR was calculated as 76 ml/min/1.73m$^2$. Left ventricular hypertrophy, left ventricular diastolic dysfunction were detected in echocardiography, and the ejection fraction was 60%. In the ambulatory blood pressure monitoring of the patient, the mean blood pressure at night was 160/100 and the mean blood pressure during daytime was 170/120 mmHg. Three antihypertensive drugs, one of which was a diuretic, were initiated for the patient. There were no significant differences between the blood pressures measured in four different extremities. Since blood pressure was not adequately controlled, 25 mg of carvedilol was added to her treatment. After psychiatric consultation antidepressant treatment with sertraline derivative was initiated. Spironolactone 50 mg was added to the treatment of the patient whose

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blood pressure did not return to the desired level during the follow-up. Meanwhile, to investigate the causes of secondary hypertension, abdominal ultrasonography, renal artery doppler ultrasonography, abdominal MRI, renal MR angiography were performed. Serum aldosterone and renin levels and catecholamine levels in 24-hour urine were measured in addition to the existing laboratory tests. No pathology was found to play a role in the etiology of secondary hypertension in the examinations. Dapagliflozin 10 mg, which is known to have a blood pressure lowering effect, was added to the treatment of the diabetic patient. It was observed that the blood pressure values of the patient, who was called to the outpatient clinic after 2 weeks, were around 150-140/90mmHg.

**Disccussion**

Resistant hypertension (RHT) is a multifactorial disease associated with several target organ damage such as microalbuminuria, left ventricular hypertrophy and arterial stiffness. Sodium glucose cotransporter 2 (SGLT-2) inhibitors have shown positive results in blood pressure levels, body weight and glycemic control in diabetic and hypertensive patients. Sodium glucose co-transporter 2 inhibitors lower blood pressure through osmotic diuresis and may be considered in diabetic patients with resistant hypertension. Given the significant cardiovascular mortality burden of resistant hypertension, there is a need for new treatment approaches that reduce blood pressure and at the same time improve cardiovascular outcomes [4]. Rather than inventing new classes of antihypertensive drugs, another strategy is to take advantage of existing classes of drugs that have proven efficacy in lowering blood pressure. As a "diabetes drug", Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to improve renal and heart failure, in addition to reducing renal glucose reabsorption and increasing urinary glucose excretion. Possible mechanisms underlying clinical benefits are hypothesized to be through natriuresis, reduction in blood pressure, weight loss, improvement in arterial stiffness, and uric acid levels, in addition to the above. In a 12-week study, empagliflozin (10-25 mg per day) was shown to lower 24-hour SBP and diastolic BP (DBP) by approximately 3-4 and 1-2 mm Hg, respectively [4]. SGLT2 inhibitors have been shown to reduce 24-hour ambulatory systolic blood pressure by 3.7(95% CI 2.3-4.2) and diastolic blood pressure by 1.8(95% CI 1.3-2.4) mm Hg compared to placebo [6]. It is considered that patients with increased salt sensitivity could potentially benefit more from SGLT2 inhibitors to lower blood pressure due to their natriuretic and osmotic diuretic effects [4]. In a post hoc analysis of EMPA-REG OUTCOME, Ferreira *et al*. investigated the effects of empagliflozin in patients with presumed resistant hypertension [7]. In this study, 22.5% of patients meet the definition of resistant hypertension, the mean difference in SBP from baseline to week 12 relative to placebo was -4.5 (95% confidence interval, -5.9 to -3.1) mm Hg at RHT ($P < 0.001$) and -3.7 (-4.5, -2.9) mm Hg in patients without RHT ($P < 0.001$). SBP was controlled more frequently with empagliflozin than placebo (<130/80 mm Hg). Interestingly, patients with RHT had 1.5 to 2 times higher risk of hospitalization for heart failure, incident/worsening nephropathy and CV death [8]. Because of these dual effects, they reported that empagliflozin is a possible option to consider in patients with hypertension and T2DM [8]. It is thought that the blood pressure reduction achieved with SGLT2 inhibitors is less compared to spironolactone (8.7 mm Hg SBP reduction with spironolactone in the PATHWAY-2 study).

This case demonstrates several important points regarding the evaluation, management of RHT and also underlines the the complexity involved in determining the mechanisms of resistant hypertension in diabetic patients. RHT is difficult to manage due to the complex interaction between sodium and fluid retention, the renin-angiotensin-aldosterone system, and activation of the sympathetic nervous system, and those at high risk of cardiovascular disease [4]. For this reason, SGLT2 inhibitors, which reduce blood pressure as well as improve cardiovascular and renal morbidity and mortality, may be promising in appropriate clinical conditions in diabetic patients with resistant hypertension. In an 8-week study with type 1 diabetes, empagliflozin was shown to reduce arterial stiffness as assessed by measuring pulse wave velocity and augmentation index [8]. Due to their mechanism of action independent of insulin, SGLT2 inhibitors reduce blood pressure and improve glycemic control while avoiding the potential risks of increased insulin doses such as hypoglycemia, hypertension and weight gain. Although aortic pulse wave velocity is generally considered the "gold standard" in non-invasive assessments of arterial stiffness, pulse pressure (PP) determined by cardiac output and stiffness of elastic central arteries can be used as a surrogate marker in clinical practice. PP can be calculated as the difference between systolic BP (SBP) and diastolic BP (DBP) [9]. Chilton et al. in a post hoc analysis of data from a phase III study in T2DM and hypertensive patients receiving 12 weeks of empagliflozin and four phase III studies in T2DM patients receiving 24 weeks of empagliflozin, they reported that empagliflozin significantly ($p<0.001$) decreased PP, MAP, and DP (or RPP) compared to placebo in both cohorts [9]. They stated that in their methodology, MAP was calculated as 2/3 DBP+1/3 SBP (mmHg); and DP (or RPP) heart rate (bpm) × SBP (mmHg) [10]. The double product (DP), also known as the rate pressure product (RPP) is calculated as heart rate × SBP and provides an indirect measure of myocardial oxygen demand [10]. Decrease in blood pressure and arterial stiffness are the possible effects of SGLT2 inhibitors

that can improve CV risk and heart failure in patients with T2DM, and it has paramount important to confirm in larger studies. An additional possible mechanistic explanation for BP reduction by SGLT2 inhibitors is local inhibition of RAAS secondary to increased sodium delivery to the juxtaglomerular apparatus [11,12].

## Conclusion

Although SGLT2 inhibitors do not have antihypertensive indications, mild blood pressure reductions observed during SGLT2 inhibitor therapy may provide an extra clinical advantage for patients with T2DM and resistant hypertension as well as improving glucose control. Finally, close follow-up of these patients is important and should include periodic laboratory testings.

*Conflict of interest statement.* None declared.

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