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Possible Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors for Reducing Effects of Blood Glucose and also Blood Pressure

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Abstract

Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) has been in focus for the pharmacotherapy of diabetes. SGLT2i contributes to decreasing blood pressure (BP) to some degree. BP changes were analyzed in 4 well-known mega-studies. They are Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study, Canagliflozin cardioVascular Assessment Study (CANVAS), Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and Dapagliflozin Effect on CardiovascuLAR Events (DECLARE)-TIMI 58. The ultimate goal of antihypertensive and hypoglycemic agents is not the achievement of target values, but the suppression of cardiovascular events. SGLT-2i show excellent strategy for event suppression and adjunct method for hypertension.

Keywords

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors, Phlorizin, Antihypertensive Agents (AHA), Cardiovascular Event, Blood Pressure

Abbreviations

CANVAS: Canagliflozin cardioVascular Assessment Study, CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, DECLARE-TIMI 58: Dapagliflozin Effect on CardiovascuLAR Events-TIMI 58, EMPA-REG OUTCOME: The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose study

Diabetes is a medical and social problem in every country and region worldwide [1,2]. One of the basic treatment methods is adequate diet [3,4]. The authors have applied a low carbohydrate diet (LCD) to thousands of patients for years and have reported its significant effects [5,6]. Specifically, we have promoted 3 types of LCDs, which are super-LCD, standard-LCD, and petite-LCD. Further, we have socially promoted the social movement of LCD through Japan LCD Promotion Association (JLCDPA) [7]. On the other hand, the other treatment method is pharmacotherapy. Recently, Sodium-glucose

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Cotransporter-2 Inhibitors (SGLT2i) has been introduced to clinical practice [8]. The mechanism of the agent had not been seen formerly, and its excellent effect has been widely known.

As a matter of fact, LCD and SGLT2i have something valuable in common. The former means trying not to put sugar-rich foods into the body through the mouth. On the other hand, the latter means a mechanism of excreting a large amount of sugar from the body through the urinary tract. The common idea is to avoid involvement with carbohydrate metabolism [9]. In recent years, there have been various studies concerning the adverse effects of carbohydrates on the human body. Carbohydrate load increases the risk of non-communicable diseases (NCDs) such as obesity, diabetes, hypertension, and dyslipidemia. SGLT2i has been reported to have the function of lowering blood sugar in diabetes and also lowering blood pressure [10]. In this article, a general overview of SGLT2i and the effect on blood pressure would be described.

From a historical point of view, the technology for extracting the medicinal component was advanced such as alkaloid from the plant in the 19th century. Among them, phlorizin contained in the bark of apple was clinically used as an antipyretic drug in a small dose [11]. After that, a high dose was proved to excrete sugar from urine. In the latter 20th century, the presence of sodium-glucose co-transporter (SGLT) in the proximal tubules of the small intestine and kidney was proposed. Successively, SGLT-1 in the small intestine and SGLT-2 in the proximal tubule was discovered [12]. Consequently, the physical action point of phlorizin was clarified, and the development of hypoglycemic agent due to the urinary glucose excretion was started related to phlorizin.

SGLT-2 inhibitor is a type of glycoside similar to phlorizin because of its chemical structure. It has glucose as a part of its structural formula and inhibits SGLT-2, which has glucose as an in-vivo organ, from the tubular side in a reversible and glucose competitive manner. Due to this structural formula and high SGLT-2 selectivity, it is considered that there is no site of action other than SGLT-2 in the proximal tubule at clinical pharmacological blood concentrations [12].

SGLT-2 inhibitor is a type of glycoside similar to phlorizin. It inhibits SGLT-2 from the tubular side in a competitive manner. Due to the structural formula and high SGLT-2 selectivity, SGLT-2i can only act at the proximal tubule at clinical pharmacological concentrations [13]. From various studies, SGLT-2i can cause not only urinary glucose excretion but also several suppressive actions on the cardiovascular event including the effect of lowering blood pressure.

There have been four well-known studies concerning SGLT-2i, which were EMPA-REG OUTCOME, CANVAS, CREDENCE, and DECLARE-TIMI 58 (**Table-1**) [14-17]. The antihypertensive effects of them are summarized. Among them, T2DM patients for secondary prevention are mostly provided by antihypertensive agents (AHA) together. Average BP before studies were 135-140 mmHg during systole and 77-78 mmHg during diastole. With adding SGLT-2 inhibitors, BP was changed -4 mmHg for systole and -1 mmHg in diastole.

The precise mechanism of reducing BP remains unclear. However, this antihypertensive effect may be obtained from some osmotic diuresis associated with urinary glucose excretion, suppression of sodium reabsorption. As a result, ATP consumption in the proximal tubule may be suppressed, and then sympathetic nerve excitation may be suppressed. The degree of urinary glucose excretion is known to depend on the renal function and blood glucose level of the subject. There were two studies using canagliflozin, which were CREDENCE and CANVAS. In the former, renal protective effect was examined in cases of renal function deterioration, where the degree of blood pressure reduction was lower compared with that of CANVAS.

From these results, the usefulness of SGLT-2i for BP control would be considered [10,18]. The degree of BP-lowering effect was not so large. The goal of SGLT-2i was not the achievement of reducing effect, but the suppression of cardiovascular event. Consequently, diabetic patients on SGLT-2i seem to have clinical benefits in the light of decreased blood glucose, blood pressure, and the possibility of a cardiovascular event.

Table-1: Lowering effect for blood pressure in trials of SGLT2 inihibitors

Trials	Medicine	eGFR	Systolic	BP	Diastolic	BP	Reports
		mL/min/1.73m^2	average (mmHg)	changes (mmHg)	average (mmHg)	changes (mmHg)	
EMPA-REG OUTCOME	Empagliflozin	76	135.5	-4	77	-1	Zinman 2015
CANVAS	Canagliflozin	77	137	-3.9	78	-1	Neal 2017
CREDENCE	Canagliflozin	56	140	-2.4	78		Mahaffey 2019
DECLARE-TIMI58	Dapagliflozin	85	135	-2.7	78	-0.5	Wiviott 2019

EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose, CANVAS: Canagliflozin cardioVascular Assessment Study, CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, DECLARE-TIMI 58: Dapagliflozin Effect on CardiovascuLAR Events

There was The Yokohama Add-On Inhibitory Efficacy of Dapagliflozin on Albuminuria in Japanese Patients with Type 2 Diabetes Study (Y-AIDA Study) [10]. As the results of 85 patients for home blood pressure on 24 weeks later, changes in the morning, evening, and nocturnal home BP showed - 8.3/- 4.2 mmHg, - 9.6 /- 4.5 mmHg, - 2.4/- 1.2 mmHg (all $p>0.05$). In addition, the reduction in urine albumin-to-creatinine ratio (UACR) has a significant correlation with the BP improvement profile [10].

A close relationship was found between BP changes and proteinuria. In T2DM, BP variability was associated with urinary albumin elevation, which is independent of other factors [18]. Consequently, control of home BP may lead to a potential therapeutic method for T2DM patients.

Similar to this article, Kluger had compared the clinical effect on a cardiovascular event for 4 main studies, in which data of CREDENCE study are from Berkovic et al. [19,20]. Four studies are DECLARE-TIMI 58, CANVAS, EMPA-REG OUTCOME, and CREDENCE. As the result of drug and placebo in each study, relative risk reduction of renal outcome event was 47%, 40%, 46%, 30%, and of major adverse cardiovascular (CV) event was 7%, 14%, 14%, 20%, respectively [19]. Consequently, glomerular filtration function and albuminuria value have been the most important indicators of clinical risk for renal and cardiovascular events. SGLT2i may give the greatest beneficial influence to these two factors.

SGLT2 inhibitor empagliflozin was given to 2286 T2DM for 24 weeks and changes of BP were analyzed [21]. In cases with lower eGFR, reduced systolic blood pressure (SBP) was maintained. Compared with placebo, change in SBP was -3.2 mmHg, -4.0 mmHg, -5.5 mmHg, -6.6mmHg in cases with 4 group of eGFR as >90, 60-89, 30-59, 30> ml/ min/1.73m^2, respectively.

In summary, the important points from the mentioned above are summarized below:

1) SGLT-2i have excellent cardiovascular event inhibitory action. Due to its structural characteristics, it has no action points in vivo other than SGLT-2 of the proximal tubule.
2) Various studies have reported multifaceted effects on human beings associated with urinary glucose excretion. Although the blood pressure-lowering effect was limited in the cardiovascular outcome studies, SGLT-2i seems to have beneficial clinical efficacy.
3) The ultimate goal of antihypertensive and hypoglycemic agents is not the achievement of target values, but the suppression of cardiovascular events. The administration of SGLT-2i would be also an excellent strategy for

event suppression and as an adjunct to antihypertensive treatment.

4) Trials of SGLT-2i for heart failure, renal failure, NASH, etc. in non-diabetic patients are also in progress at present.

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Conflict of Interest

The author has no conflicts of interest to declare.

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