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COMMENTARY

To overcome two diseases with one pill

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Hypertension and type 2 diabetes mellitus and/or obesity often coexist. Diabetes and obesity sometimes cause drug-resistant hypertension. Moreover, several antidiabetic drugs such as sulfonylureas, glinides and glitazones, as well as insulin increase body weight and often make it difficult to manage body weight in diabetic patients. Therefore, hypertensive patients with diabetes are not only at higher risk for cardiovascular disease, but also require multidrug therapy for better management. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of diabetic medication that target renal reabsorption of glucose and promote normal glucose levels associated with weight loss, and act as osmotic diuretics, resulting in lowering of blood pressure (BP). Clinical benefits of SGLT2 inhibitors have been reported recently. For example, Tikkanen *et al.*[1] reported that an SGLT2 inhibitor, empagliflozin, was associated with significant and clinically meaningful reductions in BP and HbA1c level compared with placebo in hypertensive patients with diabetes. Moreover, very recently, a placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME) demonstrated that type 2 diabetic patients treated with empagliflozin showed a lower rate of the primary composite cardiovascular outcome and of death from any cause as compared with placebo,[2] proving that SGLT2 inhibitors have a beneficial effect beyond glycemic control. The BP reduction of ~4 mm Hg in the empagliflozin group compared with the placebo group shown in supplemental data of this article may be involved in the SGLT2 inhibitor-induced reduction of cardiovascular risk; however, the details are not elucidated to date.

In the present study, Takeshige *et al.*[3] demonstrated a preventive effect of empagliflozin on abnormal circadian rhythm of BP in salt-treated obese Otsuka Long Evans Tokushima Fatty (OLETF) rats. One of the mechanisms of the improvement of BP circadian rhythm by empagliflozin treatment is a reduction of water retention. As shown in this study, empagliflozin treatment prevented the elevation of 24-h mean arterial pressure (MAP) compared with vehicle treatment, mainly due to reduced MAP in the 'inactive period', suggesting that reduced volume retention by empagliflozin has an important role in BP reduction during the sleeping time, such as nocturnal BP in humans. Recently, nocturnal BP has been highlighted. Mean nocturnal BP level is the most sensitive predictor of cardiovascular morbidity and mortality. The pathophysiology of nocturnal BP increase is multifactorial, such as volume retention, sympathovagal imbalance and disturbed breathing during sleep etc., as reviewed by Yano *et al.*[4] High-sodium intake is directly related to water retention and disturbs the circadian rhythm of renal sodium excretion in non-dipper type essential hypertension.[5] Takeshige *et al.* also showed that treatment with empagliflozin increased urinary sodium excretion in a sodium challenge test. Therefore, natriuresis by empagliflozin may be involved in the improvement of BP circadian rhythm. However, in OLETF rats treated with empagliflozin, sodium excretion was increased only during the first day (0–24 h), and not during 2–3 days after sodium administration. Interestingly, Lin *et al.*[6] also reported that sodium excretion was significantly increased in db/db mice 24 h after empagliflozin treatment, but did not differ between the control and empagliflozin groups from day 2. These results suggest that the effect of SGLT2 inhibitors on natriuresis is acute and transient; therefore, other mechanisms may be involved in the change of BP circadian rhythm other than natriuresis. Our group also reported recently that renal sympathetic denervation improves glucose metabolism through an increase in the tissue glucose uptake and glycosuria induced by SGLT2 suppression.[7] On the other hand, Kim *et al.*[8] also showed that adrenaline decreased SGLT2 protein level. Cherney *et al.*[9] reported that treatment with empagliflozin reduced arterial stiffness in young type 1 diabetic patients due to pleiotropic actions of SGLT2 inhibition; however, sympathetic nerve system activity (s.d. of normal-to-normal interval, and plasma noradrenaline and adrenaline levels) was not changed. On the other hand, Takatori *et al.* demonstrated that the abnormal innervation of perivascular nerves in mesenteric resistance arteries induced by chronic hyperinsulinemia disturbs the neuronal regulation of vascular tone and may cause hypertension in OLETF rats. Therefore, SGLT2 inhibition-induced prevention of hyperinsulinemia may prevent changes in the distribution of sympathetic nerve fibers.[10] Although it is not well known whether SGLT2 'inhibition' contributes to preventing sympathetic hyperactivity or not, there may be some interactions between SGLT2 and sympathetic nerve activation.

A link between circadian clock genes and metabolic syndrome, including hypertension has been highlighted. Moreover, higher circadian genetic risk scores generated by counting the risk alleles were observed in patients with non-dipper hypertension than in those with dipper hypertension among young-onset hypertension.[11] For example, Per1 is implicated in the circadian clock controlling sodium balance through regulation of the renal epithelial sodium

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channel.[12] Takeshige *et al*. also investigated clock genes in the kidney, such as Bmal1, Per1 and Per2. The results showed no change in their expression by empagliflozin treatment. However, they did not investigate other clock genes such as Crys. Cry1/2-null mice exhibit salt-sensitive hypertension due to abnormally high synthesis of aldosterone by the adrenal gland.[13] Moreover, Kovanen *et al*.[14] reported that Cry1 genetic variants may have a role in elevated BP and hypertension. Although plasma aldosterone level was not changed in empagliflozin-treated OLETF rats in the present study, the expression of Crys after empagliflozin treatment was not investigated. Thus, the more detailed mechanism of SGLT2 inhibitor-induced improvement of BP circadian rhythm should be elucidated, including other clock gene regulation, in the future.

Medication adherence is important for reducing hospitalization due to cardiovascular disease and mortality.[15] Versatile drugs have been expected to improve adherence to evidence-based cardiovascular medication. SGLT2 inhibitors may become one of the contributing drugs for patients with hypertension and diabetes, and as a versatile drug it has to be used carefully to avoid side effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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