[Case Report]

A Case of Type 2 Diabetes with a Change from a Non-Dipper to a Dipper Blood Pressure Pattern by Dapagliflozin

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Abstract **:** Dapagliflozin, a selective inhibitor of sodium glucose co-transporter 2 (SGLT2), is a novel glucose-lowering agent that has pleiotropic actions on blood pressure and lipids. Its glucose-lowering effect is not mediated by insulin. We report a type 2 diabetic patient whose blood pressure pattern improved from non-dipper to dipper after treatment with dapagliflozin. The 60-year-old man was treated with 5 mg/day dapagliflozin, and the effect of treatment on his blood pressure (BP) was evaluated by ambulatory blood pressure monitoring (ABPM) before and at 8 and 14 days after the start of treatment. The 24-h systolic blood pressure/diastolic blood pressure decreased from 131/87 to 127/83 mmHg at day 14, with a particular decrease in nocturnal blood pressure from 123/84 to 116/75 mmHg (nocturnal blood pressure dip increased from 9.6% to 12.8%), changing from a non-dipper to a dipper blood pressure pattern. Dapagliflozin might potentially improve not only the average blood pressure, but also nighttime blood pressure from non-dipper to dipper in type 2 diabetic patients.

Keywords **:** SGLT2 inhibitors, dapagliflozin, 24 hour ABPM, dipper pattern, type 2 diabetic patient.

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Introduction

Hypertension is observed in 40% to 60% of patients with type 2 diabetes mellitus. In particular, many patients with high insulin resistance are reported to have a non-dipper blood pressure (BP) pattern [1,2], which is a risk factor for arteriosclerotic diseases such as heart disease and brain disease. Selective inhibitors of sodium glucose co-transporter 2 (SGLT2), a group of novel glucose-lowering agents, inhibit glucose reabsorption by the proximal convoluted tubule in the kidney and enhance urinary excretion of glucose, thereby lowering the blood glucose level. These inhibitors also have pleiotropic actions, one of which is a direct BP lowering action. The BP lowering action of SGLT2 inhibitors is considered a holistic result during natriuresis and inactivation of the renin-angiotensin-aldosterone system (RAAS). Although they have been consistently reported to reduce systolic BP by 2 to 5 mmHg [3], their effect on BP patterns has not been reported. We describe a patient whose BP improved after treatment with dapagliflozin, as confirmed by 24-h ambulatory blood pressure monitoring (ABPM).

Case Report

The patient was a 60-year-old man with type 2 diabetes mellitus and body weight of 72.7 kg (body mass index, 22.7 kg/m^2). His postprandial plasma glucose level was 417 mg/d*l*, and his hemoglobin A1c concen-

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tration was 11.4%. He was admitted to our department for blood glucose control. Although he had been diagnosed with type 2 diabetes mellitus approximately 12 years earlier, he had not been treated with any glucose-lowering agents. Clinical examination showed polyneuropathy, proliferative diabetic retinopathy, and stage 2 nephropathy (urine albumin/creatinine ratio, 164 mg/g Cr; estimated glomerular filtration rate, 73.5 m*l*/min×1.73/m^2), but no evidence of macrovasculopathy. His insulin secretion estimated from urinary C-peptide immunoreactivity (CPR) was 70.7 μg/day, and the glucagon loading test showed that his plasma glucose level changed from 146 mg/d*l* to 160 mg/d*l*, his serum CPR changed from 1.83 ng/m*l* to 3.34 ng/m*l*, and he had ΔCPR of 1.47 ng/m*l*. The patient was treated with 5 mg/day dapagliflozin (once daily in the morning). Urinary glucose excretion measured after the start of treatment was around 70 g/day, with urinary volume of 1500−2000 m*l*. His body weight decreased within 14 days to 68.4 kg compared with 70.7 kg at the start of treatment. His hematocrit value did not change noticeably within 14 days, reaching 40.3% compared with 40.9% at start of treatment. Blood glucose was evaluated by continuous blood glucose measurement (iPro2). The mean blood glucose level ± glucose variability before administration was 191 ± 47 mg/d*l*, but both improved to 159 ± 44 mg/d*l* at day 4, 149 ± 40 mg/d*l* at day 9, and 147 ± 27 mg/d*l* at day 13.

Twenty-four-hr ABPM was performed before and at 8 and 14 days after the start of treatment, including measurement of daytime blood pressure, nocturnal blood pressure, and nocturnal blood pressure dip. The patient was not treated with hypotensive drugs. The 24-h mean systolic blood pressure (SBP)/diastolic blood pressure (DBP) was 131/87 mmHg before treatment, but changed to 134/84 mmHg at day 8 and decreased to 127/83 mmHg at day 14. The respective daytime SBP/DBP values showed no meaningful changes (136/89, 140/87, and 133/88 mmHg), although nocturnal SBP/DBP decreased on the respective days from 123/84 to 121/77 and 116/75 mmHg. In other words, the nocturnal BP dip increased from 9.6% to 13.6% and 12.8%, respectively, changing from a non-dipper to a dipper pattern (Fig. 1). During the same period, the patient's sodium excretion rate increased from 0.37% at day 0 to 0.68% at day 8, and 0.46% at day 14, although such change was not associated with BP improvement.

Discussion

ABPM confirmed that dapagliflozin, an SGLT2 inhibitor, improved the 24-h BP and nocturnal BP, with 24-h SBP and DBP decreasing by 4 mmHg and nocturnal SBP and DBP decreasing by 7 and 9 mmHg, thus improving the BP pattern from non-dipper to dipper. Although SGLT2 inhibitors have been reported to be effective in lowering BP in previous studies [4], there are no reports on BP pattern improvement. Furthermore, the effect of SGLT2 inhibitor on blood pressure pattern is unclear, although it was reported that dapagliflozin did not change the night-time blood pressure by ABPM analysis [5].

Blood glucose variability in type 2 diabetes mellitus patients has attracted attention in recent years; it is reported to be associated with oxidative stress and dementia, and we also reported its association with vascular endothelial dysfunction [6]. Similarly, BP variation in patients with hypertension has also attracted attention; it is known that non-dipper hypertension is associated with a high risk of cardiovascular death [7]. In the present study, dapagliflozin increased nocturnal BP dip from 9.6% to 12.8%, representing a transition from non-dipper to dipper pattern. This effect has the potential to lower future vascular events and early death.

Although weight loss is known to be associated with falls in BP, it is not associated with decreased BP in patients treated with SGLT2 inhibitors [4]. What is the mechanism of the BP-lowering effect of SGLT2 inhibitors? Reduced sodium reabsorption by the proximal convoluted tubules increases sodium transport to the juxtaglomerular apparatus, thereby inhibiting part of the Renin-Angiotensin-Aldosterone System (RAAS). SGLT2 inhibitors prevented a rise in BP in diabetic rats treated with a high-salt diet [8]. In this case report, there was no relationship between BP improvement and sodium excretion. It has been reported that salt restriction and use of diuretics in hypertensive patients with high salt sensitivity improved a non-dipper BP pattern to a dipper pattern, and that non-dipper patients have abnormal urine sodium excretion and,

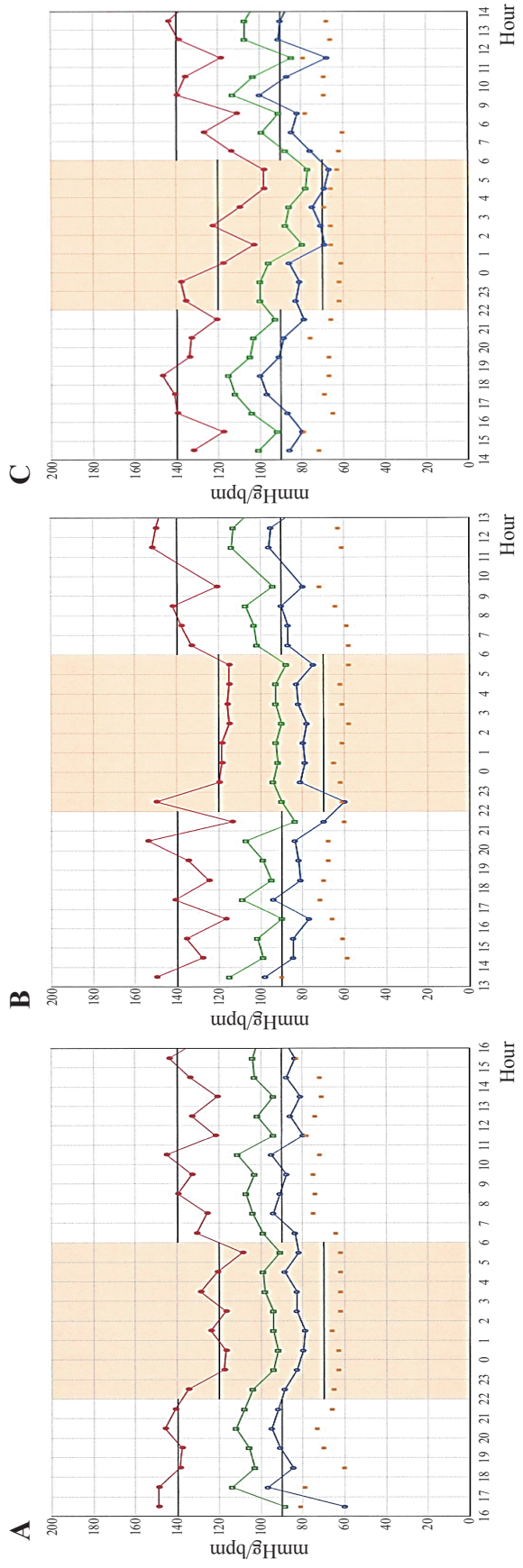

Fig. 1. Results of 24-hour ambulatory blood pressure monitoring. A: Before dapagliflozin administration, B: At 8 days after the start of treatment, C: At 14 days after the start of treatment. Shaded yellow areas represent nighttime. ● : Systolic blood pressure, ● : Diastolic blood pressure, ● : Mean blood pressure, ● : Heart rate, Horizontal lines: hypertension thresholds.

particularly, have no reduced nocturnal sodium excretion [9], indicating that excess sodium contributes to the abnormal variability in nocturnal BP. Therefore, taking into consideration the nocturnal BP drop after the administration of dapagliflozin and the BP pattern improvement to a dipper pattern in our patient, the BP-lowering effect of SGLT2 inhibitors may be related to sodium excretion. Further studies are needed to determine the mechanism of BP drop by SGLT2 inhibitors, including circadian rhythm, association with nocturnal sodium secretion, and the role of RAAS during sleep.

The present report has a limitation. The improvement of blood pressure was affected not only by the SGLT2 inhibitor but also by salt restriction. To evaluate the effect on ABPM by the SGLT2 inhibitor, we should examine ABPM data after discontinuation of the SGLT2 inhibitor.

Conflict of Interest

Dr. Tanaka has received consulting fees, speaking fees, and/or honoraria from Astra-Zeneca. Dr. Okada has received consulting fees, speaking fees, and/or honoraria from Astra-Zeneca and Ono-pharmaceutical. The other authors declare no conflict of interest.

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ダパグリフロジンで血圧がnon- dipper型からdipper型に変わった2型糖尿病の1例

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要　　旨：ダパグリフロジンは, SGLT2阻害薬（selective inhibitor of sodium glucose co-transporter 2）のひとつであり, インスリンを介さずに血糖値を改善する作用機序を有する新規2型糖尿病治療薬である．その効果は血糖改善のみならず, 血圧, 脂質などへの多面的な作用がある．今回, 2型糖尿病患者にダパグリフロジンを投与し, 血圧がnon-dipperからdipperに改善した症例を経験したので報告する．60歳男性の2型糖尿病患者に対し, ダパグリフロジン5 mg/日を投与し, 血圧への影響を評価した．血圧は, 投与前, 投与後8日目, 14日目にABPM（24 hour ambulatory blood pressure monitoring）を測定した．24時間血圧は収縮期血圧：systolic blood pressure（SBP）/拡張期血圧：diastolic blood pressure（DBP）131/87 mmHgから127/83 mmHgに低下した．中でも, 夜間血圧は123/84 mmHgから116/75 mmHgに低下した．その結果, 夜間血圧下降度は, 9.6 %から12.8 %と上昇し, 血圧はnon-dipperからdipperとなった．ダパグリフロジンは平均血圧のみならず, 夜間血圧を降下させnon-dipperからdipperへ改善する可能性がある．

キーワード：SGLT2阻害薬, ダパグリフロジン, 24時間自動血圧測定, dipper pattern, 2型糖尿病．

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