DOI: 10.1111/jch.13174

LETTER TO THE EDITOR

WILEY

Understanding of hypertension and heart failure in patients with type 2 diabetes by studying effects of sodium-glucose cotransporter 2 inhibitors on plasma B-type natriuretic peptide levels

To the Editor:

The recent article by Mengden et al led us to deeply understand the mechanisms for cardioprotective effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i).[1] The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial EMPA-REG OUTCOME trial showed that one of SGLT2i—empagliflozin—induced a striking risk reduction in cardiovascular events, such as cardiovascular death and hospitalization for heart failure.[2] However, the mechanisms for cardiovascular protective effects of SGLT2i remain largely unknown.

SGLT2i improve glycemic control due to blocking reabsorption of filtered glucose by inhibiting SGLT2.[3] Previously, we systematically reviewed and reported that SGLT2i reduce blood pressure (BP) due to body weight loss and osmotic diuresis.[4] Mengden et al reported that BP control in hypertensive patients with type 2 diabetes is poor and not accurately assessed by office-based general practitioners, despite the use of ambulatory BP monitoring,[1] indicating a possibility that BP reduction may have contributed to the reduction of cardiovascular events more than expected in the EMPA-REG OUTCOME trial.[2]

To understand which factor plays a crucial role in prevention of heart failure in the early phase, after the start of treatment with SGLT2i, we studied changes in plasma B-type natriuretic peptide (BNP), which is the marker for heart failure and other parameters associated with taking SGLT2i. Briefly, we retrospectively picked patients who had taken SGLT2i and whose plasma BNP levels were measured before, and at 3 months after, taking SGLT2i. We divided eligible subjects into 2 groups: (i) the BNP-increased group and (ii) the BNP-decreased group; we then compared characteristics between the two. This study was approved by the Institutional Ethics Committee in National Center for Global Health and Medicine and was performed in accordance with the Declaration of Helsinki.

Twenty-seven patients (age, 54.5 ± 13.4 [mean ± SD] years; male/female, 15/12; body mass index, 29.7 ± 5.0 kg/m^2; systolic BP, 131.2 ± 16.3 mm Hg; diastolic BP, 78.0 ± 12.2 mm Hg; HbA1c, 8.4 ± 1.7%; BNP, 16.6 ± 21.7 pg/mL) were eligible. Plasma BNP decreased in 13 subjects (from 18.9 ± 29.0 to 10.1 ± 19.2 pg/mL) and increased in 14 subjects (from 14.6 ± 14.0 to 32.2 ± 32.1 pg/mL).

Although there were significant differences in BP between the 2 groups, and significant changes in BP were not observed, plasma BNP levels were significantly and positively correlated with systolic BP (r = .529, P = .007 by Spearman's correlation) at baseline. At 3 months after the start of SGLT2i, hematocrit levels in the BNP-increased group (40.5 ± 4.1%, P = .001) were significantly lower than the BNP-decreased group (45.6 ± 3.1%). Plasma BNP levels were negatively and significantly correlated with hematocrit levels (r = −.516, P = .006). As the analysis of changes at 3 months after the start of SGLT2i, an increase of hematocrit levels in the BNP-increased group (0.3 ± 3.5%, P = .022) were significantly smaller than the BNP-decreased group (3.0 ± 2.0%). The change in plasma BNP levels was negatively and significantly correlated with change in hematocrit levels (r = −.659, P < .001).

Although SGLT2i may improve metabolic risk factors such as dyslipidemia,[4] it is unlikely that the reduction of hospitalization for heart failure in the early phase, after start of SGLT2i, can be explained by an improvement in metabolic risk factors. Hemodynamic factors such as reduction of blood pressure, vascular resistance, and osmotic diuresis, may be more likely to reduce hospitalization for heart failure.

A significant and positive correlation between plasma BNP levels and systolic BP at baseline suggests that reduced BP may be associated with prevention of heart failure by SGLT2i. Higher hematocrit levels in the BNP-decreased group and a negative correlation between plasma BNP and hematocrit levels 3 months after the start of SGLT2i indicate that osmotic diuresis may play an important role in prevention of heart failure in the early phase after the start of SGLT2i. Recently, increased plasma glucose was reported to lead to an adrenergic burden that can explain vascular dysfunction,[5] suggesting that plasma glucose-lowering by SGLT2i might also contribute to a reduction of cardiovascular events.

We have to mention the limitation of our study. The number of subjects was small. To elucidate our hypothesis, further studies, preferably with larger numbers of subjects, will be needed.

In conclusion, reduced BP, osmotic diuresis, and improved neurovascular dysfunction, due to SGLT2i, may play an important role in prevention of heart failure in the early phase, after the start of SGLT2i, in patients with type 2 diabetes.

CONFLICT OF INTEREST

None to declare.

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