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Letter to the Editor

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Is an Increase in Serum Magnesium One of the Causes of Cardiovascular Events Reduction in the EMPA-REG OUTCOME Study?

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To the Editor

The EMPA-REG OUTCOME study reported that a sodium glucose cotransporter-2 (SGLT2) inhibitor empagliflozin suppresses cardiovascular (CV) events in patients with type 2 diabetes [1]. It is noteworthy in this study that a reduction in hospitalization due to heart failure and death from CV was observed soon after the start of treatment. This rapid effect is difficult to explain by the slow-acting beneficial effect of empagliflozin on glucose and lipid metabolism. Various hypotheses have been proposed, and the ketone body hypothesis and hematocrit hypothesis have attracted attention [2]. Both hypotheses are expected to be tested in the future.

Previous studies have reported that serum magnesium (Mg) increased by 0.07 - 0.18 mEq/L after the start of treatment with SGLT2 inhibitors [3, 4]. The EMPA-REG OUTCOME study also showed that serum Mg increased from 1.7 to 1.8 mEq/L [1]. We paid attention to an increase in Mg. Mg acts as a coenzyme for various metabolic enzymes, and magnesium deficiency is known to have a harmful effect on blood pressure and glucose metabolism. Ninety-nine percent of Mg is present within cells and only 1% is present outside cells. Hypomagnesemia is likely to reflect magnesium deficiency in the whole body, but even if Mg is within the normal range, Mg in the whole body could be deficient [5]. The risk of CV is known to be high in hypomagnesemia.

According to the Framingham Heart Study, hypomagnesemia is a risk factor for atrial fibrillation [6]. Del Gobbo et al reported that hypomagnesemia tends to cause premature ventricular contractions, particularly in diabetic patients [7]. In addition, animal experiments showed that hypomagnesemia caused reduced cardiac function [8]. Hypomagnesemia has also been reported to increase platelet aggregation thereby facilitating thrombus formation and to enhance coronary artery constriction thereby facilitating myocardial infarction [9].

Studies involving the general population have reported that every 0.2 mmol/L increase in serum Mg reduces a risk of CV up to 30% [10]. In the EMPA-REG OUTCOME study, serum Mg increased 0.1 mEq/L (0.05 mmol/L), and therefore about 7.5% of risk reduction would be expected. The 32% suppression of CV shown in the EMPA-REG OUTCOME study cannot be fully explained by an increase in Mg. However, the EMPA-REG OUTCOME study involved diabetic patients with a history of CV, while many studies on the relationship between hypomagnesemia and death from CV involved the general population. The influence of Mg may be greater in diabetic patients with high risk of CV. I suggest that Mg increase after the SGLT2 treatment may be involved in the favorable cardiovascular events reduction; however, it has rarely been discussed. The mechanism of increasing serum Mg by SGLT2 inhibitors is unknown [3], but I think that the improvement of Mg deficiency in body tissues had a beneficial effect on the cardiovascular system.

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