

Is the Renoprotective Effect of SGLT2 Inhibitors due to their Beneficial Effect on Hypomagnesemia?

Tatsuo Yanagawa*

Department of Medicine, Nerima General Hospital, Tokyo, Japan

*Corresponding author: Tatsuo Yanagawa, Department of Medicine, Nerima General Hospital, 1-24-1, Asahigaoka, Nerima-ku, Tokyo 176-8530, Japan, Tel: +81-3-5988-2200; Fax: +81-3-5988-2250; E-mail: tyana-mj@xj9.so-net.ne.jp

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Abstract

Magnesium (Mg) deficiency is linked to diabetes and cardiovascular (CV) events. Treatment with the sodium-glucose cotransporter 2 (SGLT2) inhibitor was associated with a suppressed occurrence of CV events in patients with type 2 diabetes. We recently suggested that the increase of the serum Mg level associated with SGLT2 inhibitor treatment could explain, at least in part, the reduction of the CV events. Recently SGLT2 inhibitors have also been reported to exert a renoprotective effect and various hypotheses have been proposed regarding the mechanism. Now we would like to propose another possible mechanism, namely, the role of Mg.

Keywords: Magnesium; Sodium-glucose cotransporter 2 inhibitor; Diabetic nephropathy; Renoprotection

Magnesium Deficiency is linked to Diabetes, Hypertension and Cardiovascular Events

Magnesium (Mg) acts as a coenzyme in the insulin secretion pathway, influences the insulin sensitivity, and acts as a modulator of Na-K ATPase. Insufficient intake of Mg can cause diabetes [1] and hypertension.

Mg exerts favorable effects on the cardiovascular (CV) system, including an anti-inflammatory effect on the vascular endothelium and smooth muscle, vascular relaxant activity, and sympatholytic activity [2]. Of the total Mg content of the body, 99% is present within the cells, and only 1% is present outside cells. Thus, while hypomagnesemia reflects Mg deficiency in the whole body, Mg deficiency could be present even in the presence of serum Mg levels within the normal range [3]. Subjects with hypomagnesemia are known to be at an elevated risk of developing CV disease [4]. According to the findings of the Framingham Heart Study, hypomagnesemia is a risk factor for atrial fibrillation [5]; hypomagnesemia has also been reported to be associated with a risk of premature ventricular contractions, particularly in diabetic patients [6]. In addition, animal experiments have shown that hypomagnesemia causes reduced cardiac function [7]. Furthermore, hypomagnesemia has been reported to increase platelet aggregation, thereby facilitating thrombus formation, and to enhance coronary artery constriction, thereby increasing the risk of development of myocardial infarction [2].

A high incidence of CV events and sudden death has also been reported in patients with hypomagnesemia. A meta-analysis of relevant studies, even those including patients without diabetes, revealed that elevation of the serum Mg level by 0.2 mmol/L was associated with a 30% decrease in the risk of onset of CV disease and 40% decrease in the risk of death from CV events [8]. Adequate dietary magnesium intake has been reported to be associated with a reduced risk of cardiovascular events [9]. Thus, it might be reasonable to

conclude that the risk of CV disease/events decreases as the serum Mg concentration increases.

Mg Concentration Increases with SGLT2 Inhibitor Treatment

Sodium-glucose cotransporter 2 (SGLT-2) is expressed in the proximal renal tubules, where it reabsorbs about 80-90% of the filtered glucose. Selective and reversible inhibition of SGLT2 suppresses glucose reabsorption and reduces the blood glucose levels, independent of the insulin status.

The EMPA-REG OUTCOME study revealed that treatment with the SGLT2 inhibitor empagliflozin was associated with a suppressed occurrence of CV events in patients with type 2 diabetes, even from an early period after the start of treatment [10]. This rapid effect of the drug is difficult to explain based on the beneficial effects of empagliflozin on the glucose and lipid metabolism alone, which are of much slower onset. Various hypotheses have been proposed, and while the precise mechanism(s) remain unknown, the ketone body hypothesis and hematocrit hypothesis have attracted the most attention [11].

Previous studies have demonstrated elevation of the serum Mg concentrations after the initiation of SGLT-2 inhibitor treatment [12]. We recently suggested that the increase of the serum Mg level associated with SGLT2 inhibitor treatment could explain, at least in part, the reduction of the CV risk observed in the EMPA-REG OUTCOME study [13], because, as mentioned above, hypomagnesemia increases the risk of CV events. We and another group reported that patients with hypomagnesemia are more likely to enjoy the beneficial effects of SGLT2 inhibitor treatment on the risk of CV events, because elevation of the serum Mg was found to be more likely to occur in patients with low serum Mg levels at the baseline [14,15].

Is the Renoprotective Effect of SGLT2 Inhibitors also related to Increase of the Serum Mg Concentration?

SGLT2 inhibitors have also been reported to exert a renoprotective effect [16,17]. Several putative mechanisms have been proposed to explain this beneficial effect, such as 1) attenuation of glomerular hyperfiltration caused by the influence of the drug on the tubular-glomerular feedback mechanisms [18]; 2) workload reduction of the proximal tubules and improvement of tubulointerstitial hypoxia, which allow fibroblasts to resume normal erythropoietin production [19]. Now we would like to propose another possible mechanism, namely, the role of Mg.

In a large sample of middle-aged adults, a low total serum magnesium level was independently associated with the incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [20]. Hypomagnesemia is reported as a predictor of ESRD in patients with type 2 diabetic nephropathy [21,22]. Lower dietary magnesium intake was independently associated with greater odds of rapid kidney function decline [23]. When these findings are integrated, the renoprotective effect SGLT2 inhibitor treatment could be considered as being due to the effect of the drug in improving the serum magnesium level. However, as the above are based on observational studies, studies directly investigating the effect of Mg supplementation on type 2 diabetic nephropathy are warranted.

The mechanism of renal dysfunction caused by hypomagnesemia is still unclear, however, several mechanisms have been proposed (Figure 1); low magnesium levels have also been shown to promote renal vascular calcification [24]. Furthermore, serum magnesium levels may affect the endothelial function through exerting an influence on the thrombotic process [25], since low circulating magnesium levels have been shown to increase platelet aggregation and exert a pro-thrombotic effect. Hypomagnesemia-induced chronic inflammation [26] and hemostatic biomarkers of hypomagnesemia have been linked to atherosclerosis. An animal study indicated that Mg deficiency induces renal interstitial tubular injury [27]. I propose that SGLT2 inhibitor reduces kidney damage due to hypomagnesemia by elevating serum Mg concentration.

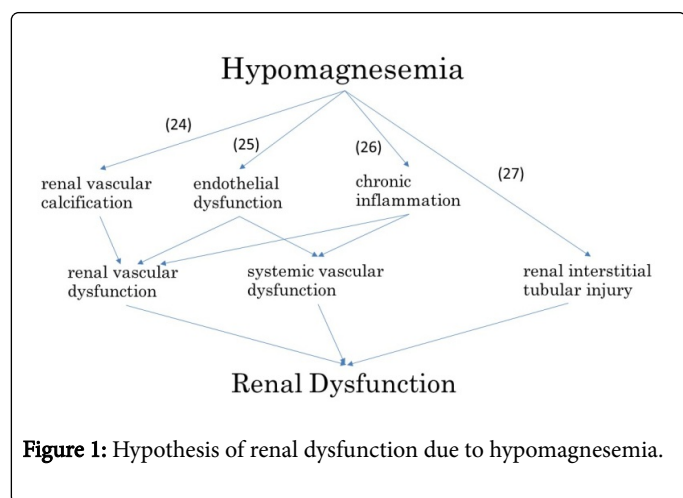


Figure 1: Hypothesis of renal dysfunction due to hypomagnesemia.

Conclusion

We would like to put forth the hypothesis that SGLT2 inhibitor therapy suppresses risk of CV events and exerts a renoprotective effect by improving the serum magnesium levels.

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