Sodium/Glucose Cotransporter 2 Inhibition and Urolithiasis: The Effect of Urinary pH and Citrate

To the Editor: In a cross-sectional study of Japanese patients with diabetes, Anan *et al.*[1] found that the use of sodium/glucose cotransporter 2 inhibitors (SGLT2is) was associated with reduced odds of urolithiasis compared to the use of other antidiabetics. They also showed reduced odds of urolithiasis among male patients without diabetes, who were prescribed SGLT2is. This finding is in line with other published studies.[2,3] Anan *et al.*[1] argue that a possible mechanism explaining this risk reduction might be an increase in urinary pH on SGLT2 inhibition. However, this assumption is not based on data and no citation of the literature is provided.

In contrast, in our *post hoc* analysis of a trial with 45 healthy volunteers, we showed a decrease in urinary pH and an increase in urinary citrate on empagliflozin (an SLGT2i) treatment over 4 weeks, which resulted in reduced supersaturation ratios of calcium-phosphate minerals.[4] We hypothesize that the decrease in urinary pH and the increase in urinary citrate, possibly resulting from decreased ammoniagenesis in proximal tubule, drive the protective effect of SGLT2is on nephrolithiasis, especially for calcium-phosphate containing stones. However, this hypothesis needs to be tested in a trial performed in stone formers.

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In Reply to "Letter Regarding 'Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Urolithiasis'"

The Author Replies: We thank Harmacek D. and Bonny O. for their interest in our study "Impact of sodium-glucose cotransporter-2 inhibitors on urolithiasis."[1] They conducted a trial with healthy volunteers and found that sodium-glucose cotransporter-2 (SGLT2) inhibitor decreased urinary pH and increased urinary citrate, compared to the effect of empagliflozin and placebo over 4 weeks.[2] This study was performed in healthy volunteers instead of patients with urolithiasis. SGLT2 inhibitor possibly increases urinary citrate, which can prevent kidney stone recurrence.

Urine of acidic pH is a common symptom presented by patients and rats with urolithiasis.[3,4] SGLT2 inhibitors increase urinary pH because of the inhibition of Na^+-H^+ exchanger and bicarbonate reabsorption in the proximal tubules.[S1–S3] In our study, urinary pH of ethylene glycol induced rats with renal calcium oxalate stone formation was significantly lowered than that of control rats.[4] In addition, phlorizin (SGLT1/2 inhibitor) treatment significantly elevated urinary pH as