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Words of Wisdom

Re: Hydrochlorothiazide and Prevention of Kidney-stone Recurrence

Dhayat NA, Bonny O, Roth B, et al.

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Expert's summary:

The authors conducted a prospective multicenter trial to investigate a dose-response effect of hydrochlorothiazide (HCT) on the composite endpoint of symptomatic or radiologic recurrence of kidney stones. In a double-blind randomization, 416 patients were given either one of three doses of HCT (12.5, 25, or 50 mg) or a placebo once daily. During median follow-up of 2.9 yr, no significant difference in stone recurrence or progression was observed among patients receiving placebo or any dose of HCT. Patients had regular clinical or telephone visits to assess symptomatic recurrence and underwent imaging with noncontrast computed tomography (NCCT) of the kidneys at the time of randomization and at the end of their follow-up period. The safety analysis revealed a higher rate of side effects such as hypokalemia, gout, new-onset diabetes mellitus, and skin allergy in the HCT groups than in the placebo group.

Expert's comments:

The management of recurrent stone formation requires a lot of commitment from both patients and physicians because of repeat follow-up visits and elaborate diagnostics. The findings from this study now question the usefulness of one of the main medications used to prevent recurrence in the majority of stone-formers, leaving a large gap in the physician's armamentarium, as major guidelines advise thiazides at a dosage of 25–50 mg/d for stone prevention in patients with hypercalciuria [1].

However, the study protocol only mentions recurrent calcium-containing stones as a key eligibility criterion and since thiazide diuretics work by reducing urinary calcium excretion, the effect of thiazide therapy could have been underestimated in this patient population. The authors even reported lower urinary calcium excretion in all of the HCT groups in comparison to the placebo group, together with a reduction in the supersaturation ratios calculated for calcium oxalate and calcium phosphate. However, the supersaturation ratio did not reach statistical significance in this unfavorable patient population. In addition, an untreated decrease in urinary citrate excretion in the HCT groups might have counteracted the effect of the medication on stone prevention. This highlights the importance of multimodal treatment, taking into account all factors related to urine supersaturation and stone formation.

Every treatment, especially those involving long-term medication, needs a lot of patient commitment as well as regular follow-up and re-evaluation by the physician. Looking at the side effects of thiazide diuretics, including hypokalemia, gout, new-onset diabetes mellitus, and a higher risk of nonmelanoma skin cancer, for example, this study clearly raises concerns about the long-term use of HCT monotherapy for stone prevention.

Do we have alternatives? There are several promising treatment options on the horizon that need further evaluation.

SGLT2 inhibitors such as dapaglifozin reduce the risk of nephrolithiasis via several mechanisms, including an increase in urine flow [2]. In a nationwide, active-comparator new-user cohort study, Kristensen et al. [2] found a 50% reduction in the relative risk of nephrolithiasis with SGLT2 inhibitors in comparison to an alternative antidiabetic medication (GLP1 receptor agonist). Besides increases in urinary volume and dilution due to osmotic diuresis, SGLT2 inhibitors reduce serum uric acid. These findings indicate that SGLT2 inhibitor treatment may be useful in preventing nephrolithiasis in individuals with type 2 diabetes. Further prospective clinical trials are needed to determine whether SGLT2 inhibitors could be prescribed to treat nephrolithiasis specifically.

Another promising new therapy for reducing urinary oxalate levels is lumasiran, an RNA interference therapeutic currently approved for patients with primary hyperoxaluria type 1 (PH1). Lumasiran reduces hepatic oxalate production by targeting glycolate oxidase mRNA and subsequently leads to a 50% reduction in 24-h urine oxalate excretion [3]. While this treatment has been effective in PH1, ongoing trials are assessing its effectiveness in a general cohort of patients with recurrent calcium oxalate stones [4].

Established therapies such as potassium citrate are equally effective in reducing calcium and increasing citrate excretion in patients with calcium-oxalate stones and hypercalciuria [5] and should also be considered in this multimodal treatment regime.

To conclude, the findings from the study by Dhayat et al. will not overthrow our guidelines on prevention of stone recurrence, but it rightly challenges long-established recommendations and promotes our efforts to find new and effective alternatives to the increasing burden of recurrent urolithiasis.

Conflicts of interest: The author has nothing to disclose.

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Julian Veser *

Medical University Vienna, University Hospital Vienna, Vienna, Austria

* Medical University Vienna, University Hospital Vienna, Wa̋hringer Gu̇rtel 18–20, A-1090 Vienna, Austria.
E-mail address: julian.veser@meduniwien.ac.at.

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Re: Inhibition of Sodium-Glucose Cotransporter 2 Suppresses Renal Stone Formation

Anan G, Hirose T, Kikuchi D, et al.

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Expert's summary:

SGLT2 inhibitors (SGLT2i) are increasingly used for treatment of type 2 diabetes mellitus (DM2) [1]. In this cross-sectional study from Japan, the effect of SGLT2i on the prevalence of urolithiasis was evaluated among 1 538 198 patients with DM2. Patients were divided according to SGLT2i prescription status, and the occurrence of urolithiasis was calculated using ICD-10 codes. Furthermore, effect of SGLT2i was examined in animal experimental studies and in vitro in a proximal tubular cell line.

Data were collected for 909 628 men and 628 570 women with DM2. For men, the prevalence of urolithiasis was significantly lower in the SGLT2i-treated group than in the untreated group (2.28% vs 2.54%; odds ratio 0.89), whereas for women there was no difference between the groups. The experimental studies suggested that SGLT2i prevented calcium oxalate (CaOx) stone formation because of reductions in osteopontin gene expression and inflammation via inhibition of glucose uptake in the proximal tubules.

Expert's comments:

To date, this is the largest epidemiological study on SGLT2i and kidney stone formation. Although the epidemiological design has limitations, including potential inaccuracy for diagnosis, the data from the very large sample size and the conformity with previous studies clearly point towards a true therapeutic gain. Thus, according to pooled data from 20 phase 1–4 trials, in which 15 081 patients with DM2 were randomized to SGLT2i or placebo, a 40% reduction in urolithiasis events was observed in SGLT2i groups in comparison to placebo [2]. The majority of the stones that formed were composed of CaOx. Similarly, in a Danish DM2 cohort (n = 19 576) it was found that treatment with SGLT2i in comparison to traditional GLP1 receptor agonists reduced the urolithiasis rate by 50% [3]. In these studies, SGLT2i seemed to protect against stone formation in women as well. The reason why there was no difference between women with and without SGLT2i treatment in the Japanese study may be because of lower urolithiasis prevalence among Japanese women.

These studies all focused on individuals with DM2, and it is still unknown whether the stone-protecting effect of SGLT2i also applies to individuals without diabetes. Experimental data and clinical observations certainly suggest a direct preventive effect of SGLT2i on CaOx stone formation, and thus the accumulated data call for randomized controlled trials evaluating stone formation as a primary outcome measure and potential adverse effects, such as urinary infections induced by glucosuria. The exact mechanisms underlying stone prevention by SGLT2i also need attention [4]. An increase in urinary flow rate due to osmotic diuresis from glucosuria and natriuresis [2–5], higher citrate excretion [5], and reduced inflammation have all been suggested.

Conflicts of interest: The author has nothing to disclose.

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