Chlorthalidone *vs.* potassium citrate in a model of hypercalciuria: differential effects on stone and bone

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Nephrolithiasis is a common problem in primary care. Although usually considered as a benign condition, it has been associated with several relevant outcomes such as chronic kidney disease (1), diabetes (2), bone disease (3), cardiovascular events (4), and hypertension (5). It also has a fairly high recurrence rate (6). These long-term outcomes are of increasing interest and have aroused scientific interest on this condition. Understanding the future consequences of kidney stones is of clear clinical importance not only for patients suffering from nephrolithiasis, but also for health services and health authorities in order to manage more efficiently the public resources. From this derives the significant role of a proper treatment of renal stone disease and, more important, a careful prevention of recurrence events, especially in individuals with recurrent nephrolithiasis, where metabolic abnormalities are a common finding.

Idiopathic hypercalciuria (IH) is the most frequent metabolic disorder in patients who form calcium (Ca) kidney stones (7,8). Most patients with IH seem to have an increased gut Ca absorption coupled with decreased renal Ca reclamation (9). Because renal Ca excretion usually exceeds intestinal Ca absorption, it is not surprising that IH individuals are often affected by bone disease with decreased bone mineral density (BMD) and higher incidence of fractures (10), particularly if a low Ca diet has been set for stone prevention as was frequently done in the past.

Medical management of this metabolic disorder focuses on reducing urine supersaturation (7,11). Lifestyle and dietary habits modifications together with drug therapy play a pivotal role in stone prevention (6,12). High fluid, low salt, adequate Ca and moderate animal protein intake are the mainstay dietary approach in Ca-based stone formers. Evidence demonstrates the importance of fluids on reducing urine supersaturation and hence the risk of recurrence (13) and the role of low sodium intake in decreasing Ca excretion (14). Medications used in IH patients forming kidney stones revolves around the use of the thiazide diuretics and potassium citrate (15). These two therapeutic strategies, commonly used in recurrent nephrolithiasis, have shown good efficacy in decreasing stone formation in humans (16). The effectiveness of thiazide or thiazide-like therapy is presumed to derive from the hypocalciuric effect on renal tubule. Citrate plays a complex role in stone prevention acting both by lowering urine Ca excretion and inhibiting crystal stone nucleation. However, to date no study has yet directly compared the combined effect of these two drugs in decreasing risk of kidney stones and improving bone quality in IH disorder.

In a recent issue of the Journal of the American Society of Nephrology, Krieger *et al.* (17) verified the hypothesis that the combination of chlorthalidone (CTD) and potassium citrate (KCit) would be more effective in lowering calcium phosphate (CaP) stone formation and

improving bone quality than either treatment alone in a genetic hypercalciuric stone-forming rat (GHS). The authors randomly divided 40 GHS rats in four groups and compared KCit, CTD plus potassium chloride and CTD plus KCit supplementation to a control group (supplemented with potassium chloride). All rats were fed a fixed amount of a normal Ca and phosphorus diet. Urine were collected every 6 weeks and evaluated for Ca, phosphorus, citrate, oxalate (Ox) and supersaturation with respect to CaOx and CaP. Kidney stone formation and bone quality were ultimately assessed at 18 weeks. The authors found a decrease in urine Ca excretion and an increase in citrate excretion induced by CTD, KCit and the combined therapy; moreover, an increase in urine supersaturation of CaP, in kidney score calcification and stone formation in the combined therapy CTD plus KCit group compared with the CTD group where no stone formation was reported. CTD rats showed also higher BMD and better mechanical characteristics.

Thus, the working hypothesis was not confirmed, and CTD alone showed better efficacy in stone prevention and in improving bone quality compared with KCit therapy or the combined therapy (KCit plus CTD). This suggests that CTD should be preferred to KCit in the treatment of Ca stone formers. There could be one further reason to opt for the use of CTD in CaP stone formers since their higher risk of cardiovascular morbidities (4,5,18). In fact, this drug was shown to reduce cardiovascular mortality (19).

Krieger *et al.* study (17) has however important limitations. The GHS rat, by forming only CaP stones, is not an ideal model of the human disease where CaOx is the main type of kidney stone; furthermore, the mainstay mechanisms of human lithogenesis starting from papillary Randall's plaque or collecting duct plugs have not been described in this animal model. Another important consideration is that it is difficult to translate the amount of citrate or thiazide administered to rats with the usual regimens used in human. Actually, the doses used in this study were supramaximal compared with those used in clinical practice, i.e., >10–15 times higher for CTD and especially for KCit, >50 times higher.

However, this study is interesting since it draws attention on the differential effects of CTD over KCit on bone quality in a condition with negative Ca balance, i.e., the GHS hypercalciuric rat.

In human stone formers with and without hypercalciuria, both KCit and thiazide diuretics, the most frequently used agents to prevent stone recurrence, have demonstrated good efficacy on BMD (3,20-23). Yet, an increase in BMD does not necessarily reflect an improvement of the bone mechanical quality (24). Actually, Krieger *et al.* (17) demonstrate in their experimental conditions that while CTD increases bone strength and improves bone mechanical properties, KCit does not.

The Krieger *et al.*' paper offers another important cause for reflection. Theoretical consideration suggests possible increase in stone recurrence by alkali supplementation in CaP nephrolithiasis since the increase in urine bicarbonate excretion (induced by citrate intake) results in increase in urine pH and CaP supersaturation. The controversy on the safety of the use of citrate in stone formers is a long-time dispute, although two open trials in distal renal tubular acidosis and medullary sponge kidney, conditions at risk of CaP stones, demonstrated rather the opposite since potassium citrate decreased stone recurrence (25,26).

Krieger *et al.* offers another piece of reassuring evidence in the use of KCit in stone formers. In fact, it is comforting to observe that the huge dose of KCit administered to GHS rats in the study, though increasing CaP supersaturation, did not induce more stones in this animal model prone to CaP stone formation.

In conclusion, because of the human heterogeneity of IH kidney stone disease, we agree with the authors that there is the need for well-designed clinical trials in order to assess and confirm these results in a human clinical setting and so improving management of kidney stone disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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