Low-dose or High-dose Hydrochlorothiazide in Idiopathic Hypercalciuria Among Children?
Re: Role of High-dose Hydrochlorothiazide in Idiopathic Hypercalciuric Urolithiasis of Childhood

Dear Editor,

We read with interest the article “Role of high-dose hydrochlorothiazide in idiopathic hypercalciuric urolithiasis of childhood” by Naseri and Sadeghi. They used high-dose hydrochlorothiazide (1 mg/kg/d to 2 mg/kg/d) in hypercalciuric children and described that no study has addressed whether low doses of thiazides have a hypocalciuric effect, especially in children. We recently reported that a low dose (0.5 mg/kg/d) of hydrochlorothiazide may be safe and effective in controlling renal hypercalciuria in children and found that hematuria and urolithiasis gradually resolved in accordance with the improvement of hypercalciuria.

Although Naseri and Sadeghi did not mention the mechanisms of hydrochlorothiazide, extracellular volume contraction resulting in a compensatory increase in renal proximal sodium reabsorption with passive paracellular calcium reabsorption and transient receptor potential vanilloid 5 (TRPV5) might be important in understanding the hypocalciuric effect of hydrochlorothiazide. Hoenderop and colleagues showed active calcium reabsorption in the distal convoluted tubule was completely abolished in TRPV5 knockout mice, and Jang and colleagues recently demonstrated that the hypocalciuric effect of hydrochlorothiazide might be associated with increased protein abundance of TRPV5 in high-salt or calcium-diet-induced hypercalciuric rats.

Therefore, we speculate that the degree of response to hydrochlorothiazide might be different in relation to not only dietary factors such as sodium intake, but also TRPV5-related mechanisms. Further studies are necessary to evaluate the role of TRPV5 in children with idiopathic hypercalciuria and elucidate whether there is a relationship between the dose of hydrochlorothiazide and abundance of TRPV5.

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REPLY BY AUTHORS
Dear Editor,

Choi and colleagues retrospectively analyzed idiopathic hypercalciuria in 28 children to evaluate therapeutic effect of hydrochlorothiazide. They used a low dose of the drug (0.5 mg/kg) in patients who mostly did not have nephrolithiasis. Thiazide diuretics are usually recommended in cases of hypercalciuria associated with urolithiasis, nephrocalcinosis, or osteoporosis. Choi and colleagues, however, used hydrochlorothiazide in patients who had urinary tract infection or hematuria due to hypercalciuria. In their series, hypercalciuria was accompanied by nephrolithiasis in 6 patients (21%), and the majority of their cases had hematuria. They found that low-dose
Hydrochlorothiazide induced normal urinary calcium excretion in the majority of patients (89%) and 11% needed high doses of the drug to reach normal urinary calcium excretion.

I think our study differs from Choi and colleagues’ study in several ways which caused different conclusions. The main differences between these two studies are as follows: (1) Choi and colleagues evaluated hypocalciuric role of hydrochlorothiazide in patients with different complications of hypercalciuria, while we studied the effect of hydrochlorothiazide in children with hypercalciuria and nephrolithiasis. (2) We defined response to treatment as normal urinary calcium excretion rate accompanied with decreased calculus size or a calculus-free condition. Choi and colleagues defined it as reaching normal urinary calcium excretion rate. (3) Idiopathic hypercalciuria is worsened by a diet high in sodium and animal protein. Thiazide diuretics lower urinary calcium excretion and promote mineral retention. Therefore, treatment of idiopathic hypercalciuria consists of high fluid intake, dietary sodium restriction, and thiazide diuretics. In addition to the role of diet in pathogenesis of calculus formation, nutritional factors such as fluid and sodium intake undoubtedly play important roles in response to hydrochlorothiazide. Neither of the studies analyzed amount of fluid and sodium intake, and thus, differences in these parameters could affect the results. (4) Another factor that could affect the results is the severity of hypercalciuria. Odvina and colleagues studied 131 patients with proven primary hyperparathyroidism and found that patients who had calculi excreted more calcium than those without calculi. In addition, they had a higher urinary saturation of calcium oxalate and brushite and excreted twice as much calcium following a 1-g oral calcium load. As our patients had hypercalciuria and nephrolithiasis, it is possible that they had higher levels of urinary calcium excretion, and thus, needed higher doses of the drug to reach normocalciuria. (5) Thiazide diuretics can potentially induce metabolic complications, especially in long-term treatment, and it is logical to consider that these complications are dose related. Overall, there is a lack of data on the metabolic side effects of thiazide treatment. Hypokalemia is the main complication that affects hypocalciuric effect of hydrochlorothiazide. Hypokalemia promotes the proximal reabsorption of citrate, which is an inhibitor of calcium oxalate and calcium phosphate precipitation. Hypocitraturia in the setting of thiazide-induced hypokalemia may counter the benefit of the decrease in urinary calcium. Therefore, differences in serum potassium levels during treatment might influence hypocaliuric effect of the drug. We recommended that serum potassium levels be checked every 3 to 4 months. In addition, to prevent hypokalemia and hypocitraturia, we added polycitra-potassium to the treatment protocol.

I think further studies are needed to evaluate whether low or high doses of hydrochlorothiazide are needed in hypercalciuric nephrolithiasis of childhood or hypercalciumia without calculus and to identify the effect of treatment on serum potassium levels in groups who receive potassium citrate in combination with hydrochlorothiazide (like our study) as compared to those who receive hydrochlorothiazide alone (Choi and colleagues’ study). Checking the volume of urine which reflects the amount of fluid intake and measuring the urinary sodium excretion several times during treatment with hydrochlorothiazide are other parameters which help to define the role of diet in patients who receive the medication.

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