### Title

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### Journal

Clinical Kidney Journal, 8(4)

### ISSN

2048-8505



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### Publication Date

2015-08-01

### DOI

10.1093/ckj/sfv048

Peer reviewed

Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

*Clinical Kidney Journal*, 2015, vol. 8, no. 4, 459–461

doi: 10.1093/ckj/sfv048
Advance Access Publication Date: 27 June 2015
Exceptional Case

EXCEPTIONAL CASE

# Hydrochlorothiazide reduces urinary calcium excretion in a child with Lowe syndrome

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## Abstract

There is a growing recognition that children with Lowe syndrome are at risk of nephrocalcinosis and nephrolithiasis from hypercalciuria. Increased fluid intake and correction of metabolic acidosis have remained the focus for intervention but are not always successful. Thiazide diuretics, which reduce urinary calcium excretion, have not been used in these children, due to concerns that (i) they may not work as a result of the underlying tubular abnormalities and (ii) their risk may outweigh the potential benefits they have to offer. Herein we report a child with Lowe syndrome who was successfully treated with thiazides in managing his hypercalciuria.

**Key words:** nephrolithiasis, thiazides, tubulopathy, urinary calcium excretion

## Background

The oculocerebrorenal syndrome of Lowe (Lowe syndrome) is a rare multisystem X-linked disorder resulting from mutations in the gene coding for an inositol 5-phosphatase, OCRL1 [1]. Clinical manifestations include ocular abnormalities (congenital cataracts, buphthalmos and nystagmus), neurologic symptoms (developmental delay, aggressive behavior, seizures and myopathy) and renal involvement. The renal involvement of Lowe syndrome is progressive and characterized by a proximal tubulopathy leading to Fanconi's syndrome [2]. Treatment of this is supportive and involves correction of acidosis and supplementation of fluid and electrolytes such as potassium and phosphorous. Over time, in most patients glomerular filtration rate (GFR) declines in a slow and progressive manner, although some patients demonstrate a bi-phasic pattern of GFR decline; the mechanism of loss of renal function remains unclear [2]. Patients with Fanconi's syndrome have generally been thought to be at a lower risk of stone formation and nephrocalcinosis in spite of having hypercalciuria (compared with those with distal renal tubular acidosis) due to their very dilute urine and elevated urinary citrate excretion [3]. However, there are some reports of children with Lowe syndrome developing nephrocalcinosis, in spite of correction of their acidosis [4, 5]. There are limited data on the use of thiazide diuretics in these children as a means to treating their hypercalciuria and preventing progression of nephrocalcinosis; moreover, concern has been raised regarding the safety and efficacy of using a medication that could further affect tubular function and lead to worsening electrolyte and fluid balance.

Herein we are reporting our experience in managing a child with Lowe syndrome who developed nephrolithiasis as a result of hypercalciuria and who was successfully managed with thiazide diuretics.

## Case description

An 11-year-old boy with Lowe syndrome, followed in the pediatric nephrology practice since the age of 7.5 years, was brought in for the evaluation of a 1-week history of intermittent gross painless hematuria (bright red urine). He was otherwise asymptomatic; although his verbal communication skills were delayed, he did

**Received:** March 23, 2015. **Accepted:** June 3, 2015

not appear in pain. His medications included 250 mg daily of phosphorous and 5 mEq/kg daily of oral potassium citrate; he had been on a stable dose of both medications for 18 months prior to his hematuria. He was polydispic and polyuric, as expected, and had nocturnal enuresis, precluding precise quantitation of his urine output. His fluid intake was estimated by his mother to be around 3 liters a day. His electrolytes, when he presented with hematuria, were normal and notable for serum potassium of 3.6 mmol/L (3.6 mEq/L), bicarbonate of 26 mmol/L (mEq/L), total calcium of 2.5 mmol/L (9.9 mg/dL), phosphorus of 1.2 mmol/L (3.9 mg/dL) and uric acid of 181.4 μmol/L (3.3 mg/dL). His estimated GFR (eGFR), based on the Schwartz calculation [6], was 1.37 mL/s/1.73 $m^2$ (82 mL/min/1.73 $m^2$); relevant urine studies included a urine pH of 8.0, an elevated random urine calcium/creatinine ratio (UCa/Cr) of 2.8 mmol/mmol (1.0 mg/mg, normal in children above the age of 7 years and in adults is <0.22 mg/mg) and a markedly elevated urinary citrate excretion at 2291 mg/g creatinine. His parathyroid hormone level, measured 9 months earlier, was 27 (normal 10–65) pg/mL; all subsequent values remained normal until after his eGFR declined. Vitamin D levels were not obtained at this time. The first vitamin D measurements were 1 year after presentation and were 62 (normal 15–75) pg/mL for 1,25-Vitamin D and 64 (normal 20–57) ng/mL for 25-Vitamin D. An abdominal radiograph and subsequent CT scan showed multiple bilateral radio-opaque stones, the largest being at the right ureteropelvic junction. The abdominal radiograph was the initial modality chosen, as opposed to an ultrasound, based on it being the most readily accessible in a rapid manner in our outpatient setting. Once the stones were noted on the radiograph, a CT scan was performed to confirm the number, size and location of the stones, in preparation for lithotripsy. For this, he underwent extra corporeal shock wave lithotripsy, initially for the right-sided stones and 4 months later for the left-sided calculi. A follow-up abdominal radiograph showed small bilateral lower pole residual calculi; a decision was made to follow these conservatively with no intervention. At last follow-up, 9 years after the first diagnosis of renal stones, this young man remains asymptomatic with stable stone burden.

Due to his hypercalciuria, he was started on hydrochlorothiazide (HCTZ) immediately after the stones were first detected. The HCTZ dose was progressively increased and amiloride was added to prevent and treat his hypokalemia. Over time, his phosphorous supplementation also needed to be increased to 375 mg daily. At last follow-up, he was receiving 5 mg once daily of amiloride (0.125 mg/kg/day) and 1.3 mg/kg/day of HCTZ. No episodes of volume depletion or worsening electrolyte abnormality were noted, with the exception of transient hypokalemia that improved once amiloride was added and on an increased potassium citrate dose. His eGFR, as expected, progressively worsened and at present is 0.67 mL/s/1.73 $m^2$ (40 mL/min/1.73 $m^2$) (at the age of 20 years).

Urine calcium studies over time evolved as follows. Following initiation of HCTZ, his UCa/Cr improved [range 0.84–1.4 mmol/mmol (0.30 to 0.50 mg/mg)]. At the age of 12 years, 2 months after his final HCTZ dose was established, his UCa/Cr continued to be mildly elevated [range 0.84–1.52 mmol/mmol (0.3–0.54 mg/mg)]. Ratios further improved after the addition of amiloride to 0.96 mmol/mmol (0.34 mg/mg) and then 0.67 mmol/mmol (0.24 mg/mg). One year after being on his stable HCTZ and amiloride doses, his UCa/Cr had normalized at 0.5 mmol/mmol (0.18 mg/mg). During this time, timed urine collections were not logistically possible due to his developmental delay and enuresis. The first 24-h urine collection that could be obtained was at the age of 15 years. This has a urine volume of 2400 mL with a creatinine excretion of 15 mg/kg/day. On this specimen, his 24-h urine calcium excretion was normal at 137 mg (3.3 mg/kg/day) with a urine sodium excretion of 151 mmol, a minimally elevated urine oxalate excretion of 40 mg (or 57 mg/1.73 $m^2$/day, normal <55 mg/1.73 $m^2$/day) and a citrate excretion that was elevated at 1661 mg/g creatinine. His urinary supersaturation for calcium oxalate was normal at 0.62 (mean 1.77), although his brushite and hydroxyapatite supersaturations were elevated at 0.39 (mean 0.21) and 9.75 (mean 3.96), respectively. His urine pH was high at 8.4, likely contributing to the elevated urinary supersaturation. At last follow-up at the age of 20 years, his urinary calcium excretion remains normal at 28 mg (0.53 mg/kg/day) on a good 24-h collection (urinary creatinine excretion of 18 mg/kg/day) and normal urinary supersaturation for calcium oxalate, brushite and hydroxyapatite.

## Discussion

Thiazide diuretics are a well-established treatment for hypercalciuria in calcium stone formers and have been shown, in long-term follow-up studied, to reduce the risk of recurrent stone formation [7]. The mechanism of action of thiazides has been extensively studied, both in animals and in humans. While much of the attention related to these agents has focused on their effects on distal tubular function, evidence from studies suggests a more complex mechanism of action. At a tubular level, it is hypothesized that by inducing mild volume depletion, thiazides increase proximal tubular resorption of water, sodium and calcium, thereby reducing urinary calcium excretion; this reduction in urinary calcium excretion has been demonstrated in an animal model [8]. In addition to reducing urinary calcium, thiazides have also been shown, by unclear mechanisms, to reduce gastrointestinal absorption of calcium and phosphorus; the net result of these is to promote a positive calcium balance in the body [8, 9]. Similar effects on phosphate retention were also noted in the same studies. Both of these effects lead to a reduction in the urinary supersaturation for calcium phosphate, as was seen in our patient. Inconsistent effects of thiazides on urinary oxalate excretion have been noted. In the genetic hypercalciuric stone-forming rat model, an increase in urinary oxalate excretion was seen and was presumed to be due to lower intestinal calcium bioavailability to bind to dietary oxalate and prevent it from being absorbed, since more of it would be bound to phosphorus present in the intestinal lumen [8]. Other studies, in humans treated with thiazides, have shown different results, with some showing a reduction in urinary oxalate excretion and others no change [10, 11]. Since our patient did not have a baseline urinary oxalate measurement, due to his inability to collect a timed urine specimen, whether he experienced a change in his urinary oxalate excretion over time could not be ascertained. However, it was reassuring that his urinary calcium oxalate supersaturation was normal on HCTZ. The mechanism of hypercalciuria in patients with Lowe syndrome is related to the proximal tubular dysfunction that is part of the underlying disease process, leading to urinary calcium wasting.

In summary, our report demonstrates the safety and efficacy of thiazide diuretics in reducing urinary calcium excretion and stabilizing the stone burden in children with Lowe syndrome. This occurred safely and in spite of an underlying tubulopathy, which may indicate that the major site of action of these agents was, at least in our patient, the gastrointestinal tract, as opposed to the tubule. The use of thiazide diuretics can be associated with hypokalemia and hyponatremia, to mention a few of their side effects, and therefore, they should be used with caution.

We feel that this case illustrates that thiazides, at least in low doses, can be safely used (or at least attempted) even in the presence of a tubulopathy such as Fanconi's syndrome, to reduce urinary calcium excretion. Whether all children with Lowe syndrome (and others with Fanconi's syndrome) who have hypercalciuria should receive a trial of thiazides to prevent stone formation or not remains to be determined.

## Conflict of interest statement

None declared.

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